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Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — 08524787001

4. Title of the invention — CRYSTALLINE AND AERODYNAMIC PARTICLES FOR PATIENTS WITH LOW INSPIRATORY FLOW RATES

5. Name of your agent *(if you have one)* — POTTS, KERR & CO.

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Signature(s) Potts, Kerr & Co. Date 11 December 2003

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CRYSTALLINE AND AERODYNAMIC PARTICLES FOR PATIENTS WITH LOW INSPIRATORY FLOW RATES

FIELD OF THE INVENTION

The invention relates to a process and the elegant, monodisperse and crystalline particles obtained, whose aerodynamic properties are exactly matched to the aspiration flow rate that was used to engineer them. The present invention uses a wide variety of aspiration flow rates that matches the inhalation flow rate of a wide variety of patients with different inspiratory inhalation efforts, thus making these particles extremely suitable for patients with high and most importantly with low inspiratory inhalation flow rates whilst depositing a high proportion of the delivered dose in deep lung. The particles of the invention also have suitable properties that enable their application in pharmaceutical and non-pharmaceutical areas.

The invention relates to a single, continuous, scalable, one step process, the particles obtained by the process, and is based on inspiration flow rate to engineer elegant aerodynamic fine particles of uniform defined geometric forms and dimensions irrespective of the substance used or it's physical state.

PRIOR ART

Techniques known in the art to obtain particles of 1-5μm are milling, crystallisation, spray-drying and supercritical fluid to name a few common examples, however these techniques are unable to produce elegant particles as described in this invention as they are fraught with problems that prevent the formation of crystalline, elegant and aerodynamic particles as briefly outlined below.

The milling process is undesirable for several reasons in that it has the potential to change more than the particle size of the feed material. The heat generated during inter-particle collisions causes changes in the solid state thereby affecting the crystallinity and stability of the milled material. Milling dramatically reduces the crystallinity of the feed material as reported, for example, with salbuterol sulphate (Ward, G.H. and Schultz, R.K. (1995). Process-induced crystallinity changes in salbuterol sulphate and its effect on powder physical stability. Pharm. Res. 12, 773-779) and microcrystalline cellulose (Ogura, K. and Sobue, H. (1970) Changes in morphology with milling of the commercial microcrystalline cellulose. J. App.

Polymer Sci. 14, 1390-1393). For the latter reductions of crystallinity of at least 23% was observed. Even synthetic polymeric macromolecules such as polyvinylpyrrolidone were damaged by milling in that it's molecular weight decreased during milling (Kaneniwa, N. and Ikekawa, A. ,1972, Influence of ball-milling atmosphere on decrease of molecular weight of polyvinylpyrrolidone powders. Chem. Pharm. Bull. 20, 1536-154), this is extremely relevant to the milling of biomolecule powders. Further, chemical decomposition of thermally labile molecules has been observed during micronisation. Furthermore, brittle materials will tend to fracture (as fracturing is a requirement for successful milling) during inter-particle collisions while ductile materials will tend to undergo plastic deformation and change shape rather than fracture (Van Vlack, L.H. (1980). Elements of materials science and engineering. Addison Wesley, Publishing, Reading, M A, pp. 185-208). Additionally, the milled powder is highly cohesive, forming agglomerates that are very difficult to mix due to poor and incomplete dispersion of agglomerates into their single particles. Milling, also, generates a significant fraction of unwanted under-size particles. The under-size material, if it remains, is considered wasted and should preferably be removed, thus making the milling process uneconomic. Other important aspects are that milling does not give the user control over the aerodynamic properties of the particle, particle density, particle shape and particle surface texture. Furthermore, the milling process exposes the personnel to the hazardous effect of the fine dust coupled with high product loss.

Conditioning has been reported in the literature (Patent WO 95/05805; US Patent 5,562,923; US Patent 5,874,063) as a method to remove amorphous content that may have been generated by a milling process. Conditioning, as reported in these patents involved treatment of fine dried material with a solvent in the vapour phase, without affecting the aerodynamic properties and other specifications of the particle (for example particle size, particle shape, presence of oversize and under-size particles, presence of particle agglomerates, irregularities in particle shape and surface texture such as sharp edges etc) by this treatment. The authors of the patents WO 95/05805 and US Patent 5,874,063 provided no details of any changes in surface properties or shape of conditioned particles. Thus, if the particles before conditioning contain any undesirable properties, such as for example undersize or oversize particles or presence of crevices, asperities, sharp edges or clefts, these will still remain in the final conditioned particles. As a result the conditioned powder is still not optimal for

use, but will instead need further treatments to obtain powder with the desired properties such as shape for example in which case a further treatment step of spheronisation, as described in US patent 6,287,540 or US patent 5,551,489 was used. Further, conditioning the powder using water or organic solvent vapour is a time consuming process taking up to 100 hours or more. Additionally, the powder bed that is being conditioned is usually static or inverted from time to time, as a result all the powder is not contacted with the vapour to the same amount, to the same extent nor in an uniform manner and thus it is also an inefficient process. The end point of conditioning is based on "guess estimation", thus any excess solvent may cause clumping between particles thereby increasing the particle size and size range. Importantly, conditioning "probably rearranges the outer surface layer of the crystals of the amorphous substance" (U.S Patent 5,562,923) whilst the interior of the particles remain amorphous. Consequently, the final conditioned particles are partially crystalline and thus unstable and will revert to the more stable form depending on the storage conditions.

US Patent 2002/0168395 A1 is another conditioning technique and describes a process for effecting a solid-state crystallization of spherical shaped microspheres produced by spray congealing. The microspheres were crystallised in an atmosphere saturated with the vapours of a solvent or non-solvent. The recovered microspheres were crystalline, but retained their size and shape after treatment. The authors gave no examples of particle size before and after treatment. Again, this technique still suffers from the draw-backs of the conditioning techniques described above.

In order to alleviate the long treatment times and potential particle fusion problems associated with conditioning in patents such as WO 95/05805, Patent WO 99/34778 discloses a process of stabilising powders using wet suspension. The particles are suspended in a suspending agent, followed by evaporation of suspending agent to harvest the particles. This technique has many drawbacks, one of which is the toxicity of the suspending agent, such as n-heptane and n-hexane used in WO 99/34778. WO 99/34778 also mentioned the use of N-alkanes such as methanol, ethanol, acetone and the like. These N-alkanes, are known to be non-solvents for the drugs and carriers (lactose) mentioned in WO 99/34778 as a result crystal growth of some treated substances might occur in N-alkanes, changing not only the particle shape but also their size and size distribution. These effects are accentuated especially if heat and long evaporation times were involved as was the case in Patent WO

99/34778. Immersion of the particles in a suspending agent may ensure efficient and uniform contact between the particles and reduce the treatment time but it does not alleviate the particle fusion problems. Further-more there is the difficulty in harvesting small particles from a suspending medium.

US Patent 6 132 797 describes a conditioning process for producing sugar crystallites 'for comestibles' by contacting amorphous sugar with a liquid non-solvent. The polycrystallite sugar are not greater than 200 micrometer, their disintegration in sugar-saturated aqueous liquid provide crystallite with an average size of 10 micrometer or less. The author provided no details for disintegrating the polycrystallite, nor harvesting the crystallites from sugar-saturated liquid solution.

From the above, it is clear that micronising produces particles that have at least 4 disadvantages which are ; aggregation, amorphous content, under and oversize, irregular and non-uniform shape. It should also be equally clear that, irrespective of the conditioning technique used, conditioning attempts only to alleviate one of these disadvantages i.e. reducing the amorphous content in which case the particles still retain the remaining disadvantages. From this it is understood to those skilled in the art, that conditioning is not necessarily the best option to obtain powder with optimal physico-chemical characteristics. Another disadvantage shared by all the above mentioned patents are that all the particles remain in contact with each other at all times during the conditioning and can therefore interfere with each other. Where conditioning is performed in a liquid, harvesting conditioned particles from a liquid medium, especially where the particles are small, is a challenge in itself even without considering the problems associated with particle fusion from such treatments. Then there are further problems associated with the correct choice of liquid medium as to whether the particles are soluble or insoluble in the liquid medium causing particle growth or whether the medium affects the stability of the constituents of the particle. Additionally the powder does not meet the inspiratory flow requirements, especially, of those patients with low inspiratory flow rates.

The crystallisation process requires considerable time and energy resources and defines such economical issues as efficiency of solvent recycling, separation of waste (impurities) and consumption of raw materials. It is acknowledged that minor changes in crystallisation conditions, for example super-saturation, temperature, impurity or cooling rate can produce significant changes in the crystal and powder properties notably, particle size, shape, purity and defect structure followed by less

pronounced but significant variations in thermodynamic and mechanical properties. These effects have been recognised as the major batch to batch and source variation problems leading to inconsistencies of the final product. Crystals with uniform shape and desired size range especially between 1- 5μm are extremely difficult to achieve by crystallisation from solution as in most cases the particles grow too fast to be recovered from the liquid medium. Further, even in cases where such particle sizes can be formed and maintained, the recovery of individual un-agglomerated particles of this size from liquid is near impossible. Hence milling is then the preferred option to obtain particles of 1-5μm size range.

There are many examples of modified crystallisation from solution processes that facilitate the recovery of the formed particles one of which is U.S. Patent. No. 6,221,398. This patent describes a process for producing a pharmaceutical powder for inhalation comprising dissolving an inhalation compound in a solvent and introducing the solution containing the inhalation compound in droplet form or as a jet stream into an anti-solvent which is miscible with the solvent and which is under agitation. The particles produced were of 10 micrometer or less, however, the authors of this patents provided no details of the particle shape. To those skilled in the art the shape of the inhaled particles is important for successful inhalation therapy.

Another modified crystallisation from solution process is US Patent 6,074,441, which describes a process for producing ultrafine-crystallisation products 'for non-inhalation purposes' with an average particle diameter of < 1micrometer. The process is based on atomisation of a solution and simultaneous evaporation of the solvent to form a crystalline product. The crystallisation occurred in a gas atmosphere and the particles obtained are too small (<1μm) to be effectively retained in the lungs during inhalation.

Patent WO 94/07582 describes a dual jet crystalliser apparatus for direct and immediate crystallisation of pharmaceutical and chemical compounds. Finasteride, acetic acid and water was instantly crystallised by the dual-jet. The average particle size of the recovered crystalline product was 10-15 um in the form of hexagonal flakes. It is understood to those skilled in the art that the crystals produced are too large to be used for inhalation.

From the above, it is obvious that with crystallisation from solution it is difficult to form and recover particles in the size range 1- 5μm that are not

agglomerated, that are narrow in size and size distribution with high degree of particle uniformity. Furthermore, crystallisation is time and energy consuming and that minor changes in crystallisation conditions causes significant batch to batch and source variation problems leading to inconsistencies of the final product. Additionally, agglomerates, under size and oversize particles are obtained with the crystallisation process. Hence crystallisation can be used to alleviate one major disadvantages of milling which is amorphousness but crystallisation has difficulty resolving issues relating to crystal consistency as regards to particle shape, surface texture and under and oversize particles.

Spray drying has been seen as an alternative technique to micronisation as the shape of the particle is nearly always spherical whilst producing particles with a narrow size distribution. However, the material formed contains various degrees of amorphous regions. Such regions are often more sensitive to external conditions e.g. moisture, thus making the particles more susceptible to chemical degradation. The relatively high temperatures required to dry the droplets may facilitate product degradation making spray drying unsuitable for thermo-labile substances. Furthermore, the particles produced are always cohesive and have poor flow and hence cannot be realistically aerosolised (Kawashima, Y et al., (1998), Effect of surface morphology of carrier lactose on dry powder inhalation property of pranlukast hydrate, International Journal of Pharmaceutics, 172, 179-188). Additionally, the recovery of the material is poor as a substantial quantity of the material is vented and thus wasted, especially those particles that are very fine. Thus making spray drying uneconomic for expensive drugs.

Patent WO 02/28377 A1 discloses a process of forming rough spherical particles by a modified spray drying process in which the liquid feed stock is atomised into a heated column at temperatures below 300°C. The resulting particles were collected using a 16 kV corona discharge arc and subsequently scraped from the discharge plate. This technique is only applicable to substances present in a liquid feed stock, the high voltage used will damage fragile materials, temperatures below 300°C are claimed , however, in reality a temperature high enough to prevent re-condensation of the liquid of the feed stock is necessary and consequently results in the use of temperatures above 70°C. Additionally, since it is necessary to scrape the particles from the discharge plate this suggests that the particles are cohesive.

Another example of a modified spray drying process is US patent 6.051.257, in which an atomised liquid droplets of a liquid feed stock passed through an impactor to classify and remove droplets greater than a pre-determined size subsequently followed by passing said droplets through an elongated heating zone at a temperature from about 100°C to 300°C to dry the droplets and form spherical solid particles. This process has many limitations some of which are listed here; only liquid solutions can be used, over-size droplets are removed but under-size droplets remain, rapid drying caused by the use of high temperatures will generate amorphous nature in the dry particle, such high temperatures are unsuitable for thermo-labile and fragile materials as claimed in that patent, fusion of liquid droplets post classification will form oversize or agglomerated particles that remain in the final product and positively skews the size distribution towards the larger size and the particle shape is limited to spheres or spheroidal.

All the techniques relating to spray drying such as that described in US Patent 6,074,441, US Patent. No. 5,314,506, Patent WO 02/28377 A1, US patent 6,051,257 are limited to liquid feeds stocks. Further, the shape of the final particle is the same as the original droplet i.e. spherical. The relatively high temperatures used to dry the particles are unsuitable for thermo-labile substances. Additionally, the particles produced are highly amorphous and thus cohesive coupled with high product loss.

Of all the above processes micronising is still the predominant process for forming inhaled products despite all of disadvantages of milling as detailed above. In conventional inhalation practise, there is no prior knowledge of the inhalation characteristics of the particles used to form the inhaled product. The particles are only tested for their inhaled deposition profiles only after both post-production and post formulation. Most importantly, it is known that the inspiratory capacity of the end user, i.e. the patient, is paramount in determining the success of the inhalation dosage form. Unfortunately, the patient is only considered as a last resort at the very end of the manufacturing process. Consequently, the formulation may be useful for some patients but more importantly it will not be useful for the frequent users of the inhaled dosage forms who can only generate low inspiratory, inhalation flow rates. The common practise is to manufacture the same powder in different doses for different patients according to their age and disease state. However, if an adult with a mild airway condition , who can generate high inspiratory flow rates, cannot obtain the full dose from the inhalation dosage form. Thus how would children, the elderly and

patients with severe airway conditions, who can only generate low inspiratory flow rates, be expected to get the full dose into the lung? From this it is understood that the same formulations cannot be adapted to all categories patients and thus it is therefore necessary to review common practises. Ideally it is preferred that each inhaled dosage form should be adapted to any particular patient, unfortunately, in reality, this would be uneconomic and too expensive to achieve as there is a large number of patient categories and disease states. The preferred and economic remedy is an engineered formulation that is independent of patient inspiratory flow rate or engineering particles specifically matched to low inspiratory flow rates that give high deposition of these particles to deep lung. Hence patients that can generate much higher inspiration flow rates will have no difficulty obtaining the full dose. Ideally the inhaled particles intended for deep lung penetration should be engineered under the test conditions i.e. engineering at flow rates matching patient inspiratory flow rate whilst ensuring high deposition profile of the engineered particles and forming stable, crystalline elegant particles irrespective of the nature or the physical state (i.e. liquid or solid) of the substance. This is the object of the present invention.

BACKGROUND OF THE INVENTION

As stated in US Patent 6,060,069, " Inspiratory flow rate is the air velocity a patient generates when inhaling. In healthy adults, during tidal breathing, inspiratory flow rate is about 15 L/min, and with effort, inspiratory flow rates of 100 L/min or more are easily achievable. Inspiratory flow rate in adult patients with moderate to severe obstructive airways diseases has been demonstrated to average 25.4 L/min (ranging from 13.3 to 50.4 L/min). Asthma is an obstructive airways disease, it may have a dramatic effect on the ability of adults and children with asthma to create an inspiratory flow rate adequate to operate most DPI's currently available".

Hence for those patients who are unable to generate sufficient inspiratory flow rates (such as patient with chronic obstructive airways diseases, young children, the elderly and those with acute or chronic respiratory conditions) to activate and operate the DPI's will result in the majority of drug depositing in the throat and upper airways, where it provides little or no therapeutic benefit and may cause side-effects, when swallowed or absorbed from their site of deposition.

The conventional procedures adopted in inhalation science are:

-producing inhaled drug particles by milling (such as micronisation) or any other techniques know in the art.

-particle size measurement of the produced drug particles by laser diffraction, electrical zone sensing or any other sizing techniques to ensure that the drug particles are within the geometric size range 1-5μm. If the particles do not comply to this size range, the particles are reprocessed in order to try and achieve this size requirement. Where the particle size requirement is achieved there is no guarantee that these particles are favourable for deep lung penetration especially as the draw-backs associated with the production of fine inhaled drug particles as listed in the prior art (some of which are the amorphous content, oversize and undersize etc), prevent deep lung penetration of inhaled drug particles.

-The resulting drug particles are then formulated for Dry Powder Inhalers (DPI's) or Metered Dose Inhalers (MDI's) and then tested using any suitable inertial impaction technique, at different flow rates, to determine the aerodynamic properties of the resulting deposited particles. The powders collected from the stages of the inertial impactor are dissolved in an appropriate solvent to enable quantification of the mass on each stage using an appropriate analytical method. The formulating, testing (at different inspiratory flow rates) and analyses are time consuming and uneconomic and still does not guarantee adequate deep lung deposition at any inspiratory flow rate.

Conventional teaching and practise for producing particles for inhalation is unable, to date, to take into consideration the inhalation effort of the patient, at the time of production, to produce aero-dynamically favourable particles to suit that patient and/or the disease state whilst giving high amount of drug depositing in the deep lung. Nor can conventional teaching and practise attain elegant, crystalline, monodisperse and aerodynamic particles as those produced by this invention.

It is desirable to adopt an engineering strategy where by the solid state particles are engineered not only to form crystalline material but also enable the formation of elegant particles that are free from the draw-backs of classic conditioning such as removal of under and oversize allowing the formation of

particles with high degree of mono-dispersity, additionally, improving and targeting the aerodynamic properties of the particles. The engineering strategy ensure good dispersion and separation of the particles at a controlled inspiration flow rate whilst simultaneously, promoting the passage of the particle through a fluid at a controlled exposure rate. In being separated from each other during engineering each particle does not interfere with it's neighbours thus preventing particle clumping that leads to increases in particle size. The fact that the particles are dispersed, allow all the particles equal opportunity to meet and collect the same amount of fluid. Dispersed, individual particles can collect a substantially greater quantity of fluid at any one time, compared to un-dispersed particles, thereby, substantially reducing the exposure time between powder and the fluid. Additionally, reducing exposure time has several advantages; any fluid can be used whether it is a solvent or non-solvent for the particle resulting in partial or complete particle solubility or insolubility. Short exposure time minimises, product degradation, polymorphism transformation and the like. The product is in the dry state, hence a high product recovery is obtained. Further-more the strategy should not only remove or reduce the amorphous content it should also include a means of removing unwanted particles such as agglomerates, under size and over-size particles whilst producing elegant aerodynamic particles that have uniform size and narrow size distribution that can be targeted for any specific or a broad range of patient inspiratory flow rate and also to compensate for insufficiencies in the patient inspiratory flow rate and the resistance of the inhaler device.

The engineering strategy should be applicable to both solid and liquid feedstocks, to engineer, produce (in-situ), remedy the disadvantages present in the feed stock and can also manipulate the particle shape and produce elegant particles with a narrow size distribution and desirable aerodynamic properties, especially, if the particle is intended for inhalation. Alleviate the problems present in the existing powder produced by previous processes such as cohesion from spray dried material, narrowing the size distribution of spray dried or micronised powder, producing elegant shapes whilst ensuring crystallinity and most importantly making these powders suitable for patients with low inspiratory flow rates. One elegant particle not yet obtained in the pharmaceutical literature is cubes and cuboidal shapes. These cubes may be beneficial to act as ideal carrier, as according to Zimon's re-suspension model, where it is assumed that the drug slides laterally along the surface of the

carrier particle, before it falls off at an edge. The longer the drug particle has to travel across the surface of the carrier particle, the greater is the drag force needed to overcome adhesion and friction between drug particle and carrier particle surface (Zimon, A.D., 1982. Adhesion of Dust and Powder, 2nd edn. Consultants Bureau, New York, pp. 307-319). Since cubes have abrupt changes at the edges coupled with small cube dimension will facilitate a small distance of particle travel along the surface of the cube before the particle falls off and detaches from the edge of the cube. Drug and carrier particles in a formulation are usually irregular in shape and have random orientation thus if a carrier or drug particle changes it's orientation it will also change the amount of drug detached from one carrier particle to another carrier particle, from dose to dose and from batch to batch. The regular shape of cubes coupled with their smooth surfaces and narrow size distribution enables a more consistent detachment of adhered particles irrespective of the orientation of the cubes. Equally drugs particles made in the cubical shape because of their size and dimensions can deliver the drug to deep lung

Additionally, the current invention enables the recovery of the substantial quantity of the material normally vented and thus wasted from spray drying, especially those particles that are very fine. Enabling their retention, treatment to reduce their cohesiveness, particle size classification to remove both undersize and oversize particles whilst giving a narrow size distribution and concomitantly increasing the yield of the spray dried product. Furthermore, the process of the invention is simple, tidy and clean preventing cross contamination and reducing personnel exposure to the hazards of dust.

SUMMARY OF THE INVENTION

The present invention is original in that it enables particles to be engineered under the conditions that these particles would normally be tested (i.e. post-production) to assure the aero-dynamic properties of the resultant engineered particles. Furthermore, the particles can be engineered at any flow rate even at flow rates much below that generated by patients with chronic or acute respiratory conditions whilst producing strikingly high fine particle fraction. It is more likely that engineered particles of the present invention are more suitable for those patients with low inspiratory flow rates. Since the particles can be engineered at any specific flow rate, it is then possible to produce particles that match the inhalation flow rate of any

patient or disease state so as to target specific patient categories and specific disease states. Additionally, the engineered particles can be used to achieve local and systemic effects irrespective of the phyisco-chemical properties of the substance (for example small molecules and macro-molecules, hydrophobic, hydrophilic and combinations thereof). The particles can be engineered under different conditions (for example at ambient temperature, below and above ambient temperature) to obtain elegant aerodynamic particles of uniform defined geometric forms and dimensions. The process of the invention is rapid, is inexpensive, is scalable, produces high yield, produces high quality powder that is unattainable by any other techniques known in the art. The feedstock from which the engineered particles are obtained can be but is not limited to solid particles, solution, suspension, slurry, emulsion and micro-emulsion. Where the starting feedstock is in the form of powder the particles of the powder can be crystalline, partially crystalline or amorphous.

The particles engineered by the process of the invention show strikingly high deposition of the engineered drug particles in the lower stages of the inertial impactor (at least 90%). Additionally, the same particles engineered at low flow rates are more likely to, similarly, deposit a high amount of drug into the deep lung of a patient whose inspiratory flow rate is the same or higher than the flow rate used to produce the drug particle of the invention. From this it is evident that particles can be engineered to match the inspiratory flow rate of any given patient. Equally particles can be engineered to match the resistance of the inhaler device. Subsequently, knowledge of the patient inspiratory flow rate and the resistance of the inhaler device enable particles to engineered by the process of this invention that compensates for insufficiencies in the patient inspiratory flow rate and the resistance of the inhaler device.

Separating, classifying or sorting

Under-size material whether liquid or solid can be collected recrystallised in-situ in one of the separation chambers by providing a crystallisation medium to form larger particles that are then re-classified to increase the overall yield. Furthermore those deposited on the other stages (over-size) can also be collected and used as it is for other applications such as for example nasal delivery or be recycled to increase the overall product yield.

Irrespective of the physico-chemical properties of the substance or combined substances alone or with additives.

An additional advantage is a substance not present in the particle can be incorporated into or onto the particle during or after separation and treatment.

Oversize particles can be collected and prepared (whether by dissolving, milling) and re-suspended for re-introduction into the process of the present invention

The method can also produce carrier particles from the same feed stock by collecting undersize particles into the crystallisation medium contained in one of the separating chambers, and allow these undersize particles to grow to the required size, that may be larger than the size of the starting material making this technique suitable as a separating and crystallisation technique producing particles with high degree of mono-dispersity irrespective of the particle size and irrespective of the physoco-chemical properties of the substances of the particle, whilst producing elegant particles of desired surface properties and high product yield because of this recycling capability.

The advantage compared to the other separating techniques high-lighted above

-can deal with liquid and solid particles

-can contact droplet or the particles with a fluid before and/or during and/or after separation

- the contacting fluid can be a crystallising medium containing a substance or additive not present as a constituent of the particle i.e. flavouring agents, fragrances and the like.

-the substance or additive to contacted with the particle can be present as a liquid or vapour phase.

-separation can be carried out at negative temperatures, i.e. atomised liquid droplets solidify and are separated within the cascade impactor. The frozen droplets are then freeze dried to form hollow and micro-porous particles. Equally well the liquid particles can be arranged to freeze within a cooled separation device.

-separation can be carried out below room temperature

-separation can be carried out at room temperature

-separation can be carried out at high temperature allowing liquid droplets to solidify

-any techniques known in the art to separate particles are embodied including elutriation, sedimentation, particles to be separated in the liquid frozen, solid or liquid states.

Compared to other patents the present invention can use temperature alone, vacuum alone, or combinations thereof.

-can pass liquid droplets through the cascade impactor or size separator system then freeze the particles

Drug detachment from the surface of carrier particles depends on particles properties such as particle size, particle shape and particle surface characteristics (i.e. surface roughness and surface shape) that have been thoroughly discussed in the literature. However, drug detachment not only depends upon the above factors but also, importantly, on the orientation of the drug and carrier particles. There have been no discussion regarding the importance of drug and carrier particle orientation on the uniformity and consistency of drug detachment from the carrier and consequently uniformity and consistency of the emitted dose.

Carrier and drug particles in a formulation are in a random orientation and hence the orientation of drug particles and carrier particles will therefore be inconsistent. Additionally, the surface characteristics(such as area of the face, the shape of that face ,crevices, clefts and hence roughness) of one face of one particle may differ from the other faces of the same particle, causing variations in drug adherence not only to that particular face but also to other faces on the same particle. As a result, drug detachment from one particle differs from one face of the particle to the other face of the particle. There will also be variations in drug detachment from one particle to another particle and the situation is further aggravated if the drug and carrier are poly-disperse and also where the shape is inconsistent.

The drug particles adhered to different surfaces of the same carrier particle will detach to different extents that are dependent upon the size of the face, surface characteristics (i.e. surface roughness) and the shape of that face. One face may allow easier detachment of drug particles than another face. From here it is understood that there will be inconsistencies in drug detachment from any of the surfaces of the carrier, hence, there is inconsistencies in the detached dose hence there is inconsistencies in the delivered dose. The same concept also applies to the drug particles.

BRIEF DESCRIPTION OF THE DRAWINGS

Preferred embodiments of the present invention will be described herein with reference to the figures, wherein:

Figure 1 shows a scanning electron micrograph of smooth spray dried lactose;

Figure 2 shows a standard twin stage impinger (TSI) of Apparatus A as described in the British Pharmacopeia, BP 2001;

Figure 3 shows the mTSI illustrating the attachment of the coupling tube to the microscope stub;

Figure 4 shows a scanning electron micrograph of the general view of cubic lactose particles engineered by drawing spherical spray dried lactose particles through the mTSI , at 60 L/min containing 7ml distilled water in the upper round bottomed flask;

Figure 4.1 shows a close view, scanning electron micrograph of the general view of cubic lactose particles engineered by drawing spherical spray dried lactose particles through the mTSI , at 60 L/min containing 7ml distilled water in the upper round bottomed flask;

Figure 5 shows a close view, scanning electron micrograph of cubic lactose particles engineered by drawing spherical spray dried lactose particles through the mTSI , at 60 L/min containing 7ml of a 50:50 v/v water : ethanol mixture in the upper round bottomed flask;

Figure 6 shows a close view, scanning electron micrograph of cubic lactose particles engineered by drawing spherical spray dried lactose particles through the mTSI , at 60 L/min containing 7ml of ethanol in the upper round bottomed flask;

Figure 7 shows a scanning electron micrograph of a rough spherical particle before treatment;

Figure 8 shows a scanning electron micrograph of cubic lactose particles, from Figure 7, that were obtained by aspirating rough spherical lactose using 7ml distilled water in the upper stage of the mTSI;

Figure 9 shows a close view, scanning electron micrograph of elegant salbutamol sulphate cubes engineered by drawing spherical spray dried salbutamol sulphate particles through the mTSI, at 60 L/min containing 7ml of distilled water in the upper round bottomed flask;

Figure 10 shows a background view of lactose particles, engineered by aspiration flow rate of 20 L/min, in the lower flask of the twin stage impinger using **20ml** of ethanol;

Figure 10.1: Close view of lactose particles, engineered by aspiration flow rate of 20 L/min, in the lower flask of the twin stage impinger using **20ml** of ethanol;

Figure 11 shows a close view scanning electron micrograph of particles obtained from aerosolised wet powder at aspiration flow rate of 60 L/min;

Figure 12 shows a photograph describing the assembly of the equipment used to generate fluticasone particles at 15, 28.3 and 60 L/min;

Figure 13 shows a background view, scanning electron micrograph of fluticasone particles, harvested from stage 5 of the Andersen Cascade Impactor, obtained by atomising and aspirating (at 15 L/min) fluticasone liquid feedstock at ambient temperature;

Figure 14 shows an in vitro Deposition of engineered Fluticasone particles on the Andersen cascade Impactor plates at an aspiration flow rate of 15 L/min;

Figure 15 shows a background view, scanning electron micrograph of fluticasone particles, harvested from stage 5 of the Andersen Cascade Impactor, obtained by atomising and aspirating (at 28.3 L/min) fluticasone liquid feedstock at ambient temperature using the Andersen cascade impactor;

Figure 16 shows a background view, scanning electron micrograph of fluticasone particles, harvested from stage 5 of the Andersen Cascade Impactor, obtained by atomising and aspirating (at 60 L/min) fluticasone liquid feedstock at ambient temperature using the Andersen cascade impactor;

Figure 17 shows a background view, scanning electron micrograph of fluticasone particles, harvested from stage 5 of the Andersen Cascade Impactor, obtained by atomising and aspirating (at 60 L/min) fluticasone liquid feedstock using the Andersen cascade impactor at a temperature of 45°C;

Figure 18 shows a background view, scanning electron micrograph of fluticasone particles, harvested from stage 5 of the Andersen Cascade Impactor, obtained by atomising and aspirating (at 28.3 L/min) fluticasone liquid feedstock using the Andersen cascade impactor at a temperature of 45°C;

Figure 19 shows a background view, scanning electron micrograph of fluticasone particles, harvested from stage 5 of the Andersen Cascade Impactor,

obtained by atomising and aspirating (at 20 L/min) fluticasone liquid feedstock at a temperature of 45°C using the Andersen cascade impactor;

Figure 20 shows a background view, scanning electron micrograph of salbutamol sulphate particles, harvested from stage 1 of the Andersen Cascade Impactor, obtained by atomising and aspirating (at 60 L/min) fluticasone liquid feedstock at ambient temperature using the Andersen cascade impactor at a temperature of 45°C;

Figure 21shows the mTSI used for **example 6** showing the positioning of the pyrex tube and microscope slide;

Figure 22 shows a background view, scanning electron micrograph of BDP particles obtained by atomising and aspirating (at 60 L/min) BDP liquid feedstock at ambient temperature using the mTSI;

Figure 23 shows a background view, scanning electron micrograph of FP particles obtained by atomising and aspirating (at 60 L/min) FP liquid feedstock at ambient temperature using the mTSI;

Figure 24a shows a background view, scanning electron micrograph of a 10 to 1 ratio of FP/SML particles obtained by atomising and aspirating (at 60 L/min) FP/SML liquid feedstock at ambient temperature using the mTSI;

Figure 24b shows a close view, scanning electron micrograph of a 10 to 1 ratio of FP/SML particles obtained by atomising and aspirating (at 60 L/min) FP/SML liquid feedstock at ambient temperature using the mTSI;

Figure 25 shows a close view, scanning electron micrograph of FP particles obtained by atomising FP liquid feedstock WITHOUT ASPIRATION at ambient temperature using the mTSI.

DETAIL DESCRIPTION MATERIAL

The system of the present invention is versatile in that it engineers the particles at aspiration flow rates that match those of the patient inspiratory flow rate and tests the particles for their aerodynamic properties. The system of the current invention can comprises several engineering phases, with different cut-off diameter, which can operate as a whole or in part. In each phase the particle can be engineered in an environment that is predominantly in the gaseous state, predominantly in the vapour state, predominantly in the liquid state or combinations thereof. For the same aspiration flow rate the morphological features and aerodynamic properties of the

particle can change according to the environment within the phases of the system. Using heat to engineer the particles is not a necessity, however, the system is flexible in that all the phases of the system can be maintained at the same temperature, each phase can have a temperature that is different from other phases and all the phases can have different temperatures. When the temperature is used, the temperature can be below or above 0°C. Aspiration flow rate is used in this invention to transport, deaggregate, disperse, dictate the morphology and accelerate the formation of particles that are suited to the flow rate that generated them. Aspiration, in contrast to other mechanical means, is a non-aggressive process that is unlikely to cause damage and chemical stability problems as is normally associated with common practise such as micronisation and spray drying. The system is further versatile in that it can form particles of any size (such as fine drugs particles and large particles such as carrier for inhalation) with a high degree of uniformity and mono-dispersity irrespective of the type and nature of the substance.

Since the system enables control of different environments and temperatures in each phase it is possible for this system to thus mimic the conditions of the human respiratory tract so as to engineer particles that are not only suited to the inhalation flow rate of the patient but also the conditions of the patient respiratory tract (such as humidity and temperature).

To those skilled in the art, the aspiration flow rate can be varied or can change from one phase to another.

EXAMPLES

Engineering elegant particles from solid

Example 1: Water is a solvent for lactose and is used to engineer lactose particles.

Engineering elegant, crystalline, lactose cubes (and cuboids) at aspiration flow rates of 60 L/min using a modified twin stage impinger. The aspiratory flow rate was used to deaggregate, disperse the powder feedstock whilst simultaneously or subsequently engineering and recrystallising the solid particulates to produce elegant fine particles of uniform defined geometric forms and dimensions, produce a powder

with improved physico-chemical characteristics and aerodynamic diameter less than 6.4μm in a one step process.

5 gm of α-lactose monohydrate (Borculo-Dormo, U.K) was dissolved in 100 ml distilled water and the resulting solution was spray-dried using a Buchi 190 mini-spray dryer according to the following conditions:

Inlet temperature: 176 °C,

Outlet temperature: 112 °C,

Aspirator dial reading: 15,

Lactose solution feed rate: 5 ml/min,

The spray dried lactose was collected and stored in a desiccator over silica gel until further use. The resulting particles are shown in Figure 1, note from Figure 1, the particles of the starting feedstock is both spherical and smooth.

A twin stage impinger as described in Apparatus A of the British Pharmacopeia, BP 2001 (Figure 2) is routinely used to measure the aerodynamic diameter of airborne particles and to assess the *in-vitro* delivery of drugs for inhalation. The twin stage impinger has two impaction stages, the upper stage, a round bottomed flask, traps agglomerates and non-inhalable particles whilst the lower stage, a conical flask, is aimed to trap all the smallest particles with aerodynamic diameter less than 6.4 μm. 7ml of a liquid is normally placed in the upper stage (i.e. the round bottomed flask) to prevent bouncing of impacted particles. The cut off diameter of the upper stage at 60L/min is 6.4 μm (Miller , *N.C., Marple, V.A., Shultz, R.K. & Poon, W.S., Assessment of the twin impinger for size measurement of metered dose inhaler sprays. Pharm. Res., 1992; 9: 1123-1127).*

A modified twin stage impinger apparatus (mTSI) was developed for this invention (Figure 3). Comparison of Figures 2 and 3 shows the modification brought to the original twin stage impinger.

7ml of distilled water was placed in the upper stage of the twin stage impinger whilst the lower stage was free of any liquid. A rotahaler (GSK, Ware U.K.) was fitted into a moulded rubber mouth piece (i.e. point A in Figure 3) attached to the throat piece of the impinger. Once the assembly had been checked and found to be airtight and vertical, the aspirating pump was switched on at an inspiration flow rate of 60L/min and 100mg of spray dried lactose powder, as shown in Figure 1, was introduced using a glass weighing boat into the inlet port of the rotahaler. Two

seconds after all the spray dried lactose was drawn, the aspiration pump was switched off and the twin stage impinger dismantled to recover the microscope stub containing deposited powder and it was stored for two days before analysis using a scanning electron microscope and the results are shown in Figures 4 and 4.1

From Figure 4 and Figure 4.1 there are many strikingly important observations. The particles of the invention are elegant cubes that are perfectly smooth(without any microscopic surface defects), monodisperse, with aerodynamic diameters less than 6.4μm, are individual cubes that are separated from each other suggesting that these cubes are non-cohesive which are contrary to the spray dried starting powder and contrary to particles of that size which are invariably always known to be cohesive.

The round bottomed flask of the upper stage usually contains a liquid that prevents bouncing of airborne particles. The distilled water in the upper stage not only acts to remove agglomerated and non-inhalable particles, it also acts to moisturise (aspiration assisted absorption and/or adsorption) and thus facilitate the engineering (aspiration to partially or completely desorb the sorbed moisture) of the airborne inhalable particles. Hence, in this present invention this liquid is used as an engineering medium to crystallise and change the shape of the feedstock material (spray dried lactose). The lower stage of the twin stage impinger was free from liquid and was used to collect the engineered particles. To those skilled in the art any modifications such introducing a liquid (alone or liquid containing any substance) into the lower stage to introduce a substance to the particle, modify the attributes of the particles, application of suction to engineer particles is within the scope of this invention. The particles can be collected, dried and stored until further use or further processed by the method of the invention. The liquid in the upper stage can be a solvent for the particles to be engineered, a non-solvent, and combinations thereof. The aspiration flow rate is applied to control the form of the liquid (vapour, droplets suspended in a gas) and the amount of liquid brought to the airborne particles and also determines the residence time of the airborne particles within the form of the liquid. The aspiration flow rate controls the rate and extent of liquid desorption from airborne particles allowing particle engineering in a controlled fashion. The atmosphere in the engineering system or the atmosphere surrounding the engineering system can be loaded with the vapour or droplets of the liquid such that the liquid in the upper stage

can optionally be removed. The atmosphere can be at any desired temperature and or pressure to favour particle engineering in a controlled manner.

The liquid in the upper flask may be a boiling liquid such as a liquid maintained at is boiling point or liquefied gas such as liquid nitrogen, liquid air and the like

To those skilled in the art, a liquid can be introduced in the bottom flask of the lower stage of the engineering system so that dispersed, individual particles with aerodynamic diameter less than 6.4μm can grow independently, uniformly without interfering with it's neighbours to form elegant carrier particles that are larger than the particles of the starting feedstock. The aspiration flow rate generates turbulent flow of the gas in the flask containing the engineering liquid that serves to agitate and stir the liquid thus preventing particle clumping whilst increasing the rate of particle growth. It is also a method of utilising and growing wasted under size particles to increase the overall particle yield. By adjusting the aspiration flow rate, can adjust the turbulence within the device and thus adjust the agitation of the liquid thereby maintaining the dispersion of the particles and thus control the rate of particle growth whilst maintaining a stirring rate compatible with delicate particles that are unsuitable for mechanical stirring. Furthermore, the particles are dispersed, monosized and consequently have the same settling velocity. The settling velocity of the particles in the engineering liquid is reduced as a result of stirring caused by the turbulent air flow, hence, this maintains full contact with the liquid, preventing contact with the sides of the glassware of the device hence the particles will grow in a uniform manner whilst maintaining it's regular shape and monodispersity compared to conventional crystallisation, where fracture caused by the stirring blades and adherence of the particles to the blade causes variations within the batch and from batch to batch. The engineered particles are different in size, are larger than the starting feed stock material, the shape can be maintained (compared to the particles of the original starting material) or altered whilst maintaining the monodispersity and elegance. Particle growth can be promoted by heating the lower flask (lower stage collecting flask) containing the liquid. The surface texture of the particles can be engineered to suit the intended use. The engineered particles can be more crystalline than the feedstock. The liquid in the lower flask can contain one or be a combination of at least two liquids with and without additives.

The particles formed by using a liquid in the lower flask is rapid compared to conventional crystallisation due to the controlled and uniform agitation of the liquid caused by turbulence of air flow within the lower collecting flask caused by controlled aspiration flow rate.

The liquid used to engineer the particles may be pulled through a bed of the powder at a controlled aspiration flow rate. It should also be clear that the liquid pulled through the powder bed can also be in the vapour state to limit condensation of the engineering liquid on the particles and hence minimise liquid bridging, fusion and particle clumping. This ensures engineering of all the particles within the powder bed and removal of almost all the liquid.

Example 2

The same as example 1, except that 7ml of a 50:50 v/v water : ethanol mixture was used in the upper round bottomed flask instead of 7ml distilled water.

From Figure 5 it is clear that cubes are also formed that are elegant cubes that have elements of surface roughness. The aerodynamic diameters of these engineered particles is less than 6.4μm.

Example 3: Ethanol **is a non-solvent for lactose and is used to engineer lactose particles.**

The same as example 1, except that 7ml of ethanol was used in the upper round bottomed flask instead of 7ml distilled water

From Figure 6, it is clear that cubes are again formed that are elegant and have elements of surface roughness. The aerodynamic diameters of these engineered particles is less than 6.4μm.

Note: using a solvent (Example 1, using water) for the substance of the particle, a non-solvent (Example 3, using ethanol) for the substance of the particle and combinations of solvent and non-solvent (Example 2 using water ethanol mixture) allowed the engineering of elegant cubes whose surface can be engineered to be

smooth or rough. Additionally the engineered cubes have aero-dynamic diameter less than 6.4μm.

Spherical feedstock particles were deliberately selected as they are easy to distinguish from the elegant cubes obtained by the method of the invention.

In all the examples 1-3, the starting feed particles are amorphous, cohesive, smooth and spherical in shape yet the process of the current invention can also engineer cubes from partially crystalline or crystalline feed stock as shown in the example below..

Example 4: Starting feed-stock of lactose particles that are spherical, crystalline, non-cohesive which have rough surfaces.

The experimental procedure was the same as example 1, except that the starting feedstock is spherical, crystalline, non-cohesive lactose that have rough surfaces as shown in Figure 7.

From Figure 8 it is clear that elegant cubes which are smooth in surface are formed. Amongst the particles are cubes and a few cuboidal crystals.

To the skilled artisan, it should be apparent that the irrespective of the surface texture and the solid state of the starting feed stock the final particles are cubes and/or cuboidal.

Example 5

Starting feed-stock of smooth, amorphous, cohesive, spherical salbutamol particles.

5 gm of salbutamol sulphate was dissolved in 100 ml distilled water and the resulting solution was spray-dried in the same manner as described in example 1. The resulting spray dried salbutamol sulphate particles are spherical, smooth in surface and are highly cohesive.

The spray dried salbutamol sulphate feedstock was engineered in a similar manner to that described in example 1. Figure 9 is an example of engineered salbutamol sulphate.

The particles obtained are elegant and cubic in shape, smooth in surface.

Example 6

In the above examples a liquid was introduced into the upper flask of twin stage impinger. By introducing a liquid into the lower flask it is possible to also engineer the particles. To exemplify this **20ml** of ethanol was placed in the lower flask of the Twin Stage Impinger (the polypropylene lower jet assembly was removed) whilst the upper flask was liquid free. 500mg of spray dried lactose was aspirated at an inspiration flow rate of 20 L/min in a similar manner to example 1 except that the aspiration flow rate was maintained for two minutes after all the spray dried powder had been aspirated.

The resulting liquid in the lower flask of the Twin Stage Iminger was poured above a 0.45μm membrane filter (Whatman, Maidstone U.K) and the remaining ethanol in the liquid was desorbed from the particles by vacuum. The resulting engineered particles are shown in Figure 10.

From Figures 10 and 10.1 the particles have increased in size compared to the original starting material (as shown in Figure 1), the particles are monodisperse, uniform in size shape and are much rougher in surface texture. The particles are separated and exit as single particles in the dry state and are thus non-cohesive. Since the particles have grown in size this suggest that they are more crystalline than the starting material.

The powder was dispersed and deaggregated at a controlled aspiration flow rate which also carried them through a pre-separation zone that is free from any liquid or vapour to allow removal of agglomerated and non-inhalable particles. The resulting dispersed airborne particles were carried by the aspiration flow rate to hit the crystallisation medium (ethanol contained in the bottom flask of the Twin Stage Impinger) in a dispersed manner. The aspiration flow rate continuously mixed the crystallisation medium in a uniform manner and hence minimised sedimentation of the particles hence the particles were maintained in a suspended manner in the liquid and have equal opportunity to grow and this was confirmed by the uniformity in the particles size and shape. Furthermore, the continuous mixing prevent particle fusion as the particles that come into contact with each other have insufficient time to develop any kind of bridging between them that is the cause of particle fusion and

batch to batch variations, as shown by the scanning electron micrographs. Additionally, there was no damage to the particles, as shown from the scanning electron micrographs, suggesting that this technique is ideal for mixing and crystallising from solid or even from liquid. Since the aspiration flow rate can be easily controlled at low and high flow rates this then makes it useful for mixing and crystallising from mediums with wide range of viscosities.

Additionally to facilitate the non-destructive stirring and crystallisation resulting from aspiration flow rate, any other non-destructive stirring mechanisms such as bubbling a gas through the liquid is embodied.

Example 7

0.5gm of spray dried lactose was quickly immersed in 20ml ethanol and filtered under vacuum to remove excess ethanol to form a wet powder. The harvested wet powder was loaded into a glass delivery device that was connected to the glass throat (of the twin stage impinger) connected to the inlet port of Andersen cascade impactor. The wet powder was aerosolised at an aspiration flow rate of 60 L/min, the pre-separator of the Andersen cascade impactor free of liquid and an example of the deposited particle is shown in Figure 11.

The starting material was spray dried wet lactose with smooth surface and the final product (Figure 11) also has a smooth surface but it is larger in size compared to the original material (Figure 1).

Examples 6 and 7 make it clear that it is possible to engineer larger particles that have different surface textures.

Engineering elegant particles from liquid feedstock.

An Andersen Cascade impactor was one aspect of the engineering device to mimic as closely as possible the human airways. Different flow rates were used not only to dictate the morphology and aerodynamic properties matched to the inspiratory flow rate but also to test the particles in-situ to ensure that the particles deposit in those stages of the Andersen cascade impactor that represent deep lung. The aspiration flow rates used were matched to mimic patients with different inspiratory inhalation capacities i.e. low aspiration flow rate (15 L/min) representing patients

with severe airways conditions , medium aspiration flow rate (28.3 L/min) representing the inspiratory inhalation flow rates of patients with moderate airways condition and 60 L/min to represents the inspiratory inhalation flow rate of those patients with mild airway conditions.

Steroids represent a mainstay of airway treatment. However, deposition of sufficient quantity in the lower stages of the lungs without associated side effects is not possible as only a small fraction of the nominal dose reaches the lungs a and as the majority of the dose is swallowed causing side effect such as skin thinning, cataract, skin cancer, immune suppression and the like. In order to alleviate and minimise these side effects, it is preferable to ensure that the particles have a morphology and aerodynamic properties which suit that patient inspiratory inhalation flow rate to maximise drug deposition to the lungs. Presented in the following examples are the use of aspiration flow rate that matches the patient inhalation flow rate to dictate the particle morphology and its associated aerodynamic properties whilst testing in situ to ensure maximum deposition in the lower stages of the testing device that represents deep lungs in patients. Deposited particles in the lower stages of the testing device are more likely to be inspired and deposited in the deep lungs of a patient whose inspiratory inhalation flow rate matches that of the flow rate used to generate them.

Example 8a

Engineering fluticasone propionate particles whose morphology and aerodynamic properties are suited for patients with severe airway conditions at aspiration flow rate of 15 L/min.

1: Air compressor connected to the air brush
2: Air Brush inserted in inlet port of pyrex tube
3: 50cm pyrex tube
4: Glass throat of twin stage impinger
5: Andersen Cascade impactor
6: Aspirating pump

The Andersen Cascade impactor was used in this experiment as an engineering and particle separating device according to their aerodynamic diameters.

0.5g of Fluticasone propionate (FP) was dissolved in 50 ml of a good solvent for that substance which in this case was acetone. A good solvent is the one in which the drug is readily soluble at that concentration.

Once the assembly as indicated in Figure 12 had been checked and found to be vertical and airtight, the aspiration pump was switched on to generate an aspiration flow rate of 15 L/min. 10ml of the FP solution was loaded into the stainless steel cup of an Air brush (model SIMair XL2000 Simair Graphics Equipment Ltd, Harrogate). The atomisation head of the air brush was introduced into the inlet port of the pyrex tube and compressed air at a pressure of 2 bars (40 PSI) was utilised to atomise the FP solution at a feed rate of 11 ml/min at ambient temperature

The liquid droplets generated by the airbrush were pulled and the aerosol was sucked and the solvent desorbed from the droplets by the aspiration flow rate to dictate the morphology and aerodynamic properties of the engineered particle that suit that flow rate and testing said engineered particles for their deposition profiles at that flow rate to ensure high deposition at stages 4-7 of the Cascade Impactor that represent deep lung. The engineered aerodynamic particles are collected, dried in a ventilated oven and the resulting particles were stored over silica gel until further use. The overall yield of the collected particles was in excess of 80% and this is much higher than the yield obtained by other traditional methods such as spray drying.

From Figure 14 it is clear that there is high deposition in plates 4 to 7 of the Andersen Cascade impactor

From Figure 14, it is evident that the particles are aerodynamically favourable at that flow rate and are thus suitable for those patients with severe airway conditions and who can only generate a low inspiratory inhalation flow rate.

Example 8b

Engineering fluticasone propionate particles whose morphology and aerodynamic properties are suited for patients with severe airway conditions at aspiration flow rate of 28.3 L/min.

Using similar experimental protocols as in Example 8a, the engineered particles were engineered and tested simultaneously to ensure their high deposition and suitability at an inspiratory flow rate of 28.3 L/min. The resulting particles are shown in Figure 15.

Example 8c

Engineering fluticasone propionate particles whose morphology and aerodynamic properties are suited for patients with severe airway conditions at aspiration flow rate of 60 L/min.

Using similar experimental protocols as in Example 8a, the engineered particles were engineered and tested simultaneously to ensure their high deposition and suitability at an inspiratory flow rate of 60L/min. The resulting particles are shown in Figure 16.

The aspiration flow rate dictates the morphology to the particles as shown from figures 13-15 and 16. The particles engineered at 15 and 28.3L/min are spherical and smooth whereas, those engineered at 60L/min are less uniform with a plurality of shapes some of which have collapsed, whereas others remains spheroidal. The majority of particles present rough surface with a permeable casing.

Example 9

Heat Experiments

Example 9A

See figure 17.

Example 9b

See figure 18.

Example 9c

See figure 19.

Example 10

See figure 20.

Example 11

The modified twin stage impinger (mTSI) of Figure 3 was further modified by replacing the microscope stub with a microscope slide and connecting the outlet of a 50cm long pyrex tube (1.4cm in diameter) to the glass throat of the twin stage impinger (i.e. point A of Figure 3). At the other end of the pyrex tube is a 8mm centred hole that was the inlet port for the introduction of the liquid feedstock. This assembly is shown in Figure 10. 7ml of ethanol was placed in the upper round bottomed flask of the twin stage impinger whilst the lower flat bottomed flask was free of any liquid. 0.5g of beclomethasone dipropionate (BDP) was dissolved in 50 ml of acetone. Once the assembly had been checked and found to be vertical and airtight, the aspiration pump was switched on to generate an aspiration flow rate of 60L/min. 10ml of the BDP solution was loaded into the stainless steel cup of an Air brush (model SIMair XL2000 Simair Graphics Equipment Ltd, Harrogate). The atomisation head of the air brush was introduced into the inlet port of the pyrex tube and compressed air at a pressure of 2 bars (40 PSI) was utilised to atomise the BDP solution at a feed rate of 11 ml/min at ambient temperature.

NEED TO INSERT FIGURE OF mTSI MODIFIED WITH GLASS SLIDE AND PYREX TUBE

The BDP particles obtained are shown in Figure 22.

From the engineered particles of Figure 22, it is clear that they are spheriodal casing some of these casing have collapsed in on itself. Some of the casings are smooth in surface, some of the particle casing and interior are partially-permeable, permeable and impermeable, some of are riddled and riddled with vacuities , lacuna, empty spaces, gaps, pits, vacuoles, vents, fissures. Most of the particles have free space.

To those skilled in the art by altering the inspiration flow rate controls the residence time of engineered airborne particles, controls the aerodynamic diameter of engineered particles, controls alters the particle shape, controls particle surface and particle interior structure (for example spheriodal casing, smoothness or

roughness in particle surface, permeability of the particles, riddling and riddling of the particles with vacuities , lacuna, empty spaces, gaps, pits, vacuoles, vents, fissures and free space.). It also controls the extent of particle collapse.

Example 12:

The experimental procedure and conditions used were the same as example 11, except that the starting feedstock was a solution of 1% Fluticasone propionate (0.5g FP in 50ml acetone).

Example 13:

The experimental procedure and conditions used were the same as example 6, except that the starting feedstock was solution of a 1% mixture of Fluticasone propionate (FP) and salmeterol xinafoate.(SML) The ratios of Fluticasone propionate to salmeterol xinafolate used in the mixtures were 10 to 1, 5 to 1 and 2 to 1 w/w, respectively.

Figure 24a is a general view of the engineered particles obtained with the 10 to 1 ratio of fluticasone propionate to salmeterol xinafolate, whilst Figure 24b is a close view of these same particles.

The rationale behind this experiment was to engineer and formulate a combination FP/SML corresponding to a brand formulation (**details, manufacturer**).

From examples 11, 12 and 13 it is obvious that the process can be applied to a variety of substances hence it is not limited to the substances detailed in these examples. Furthermore the process can be used to engineer drug particles containing at least two substances. Additionally the particles produced have an aerodynamic diameter less than 6.4μm. The particles shown in examples 11,12 and 13 have similar morphological features despite using different feedstock material, the features are that they are spheriodal casing some of these casing have collapsed in on itself. Some of the casings are smooth in surface, some of the particle casing and interior are partially-permeable, permeable and impermeable, some of are riddled and riddled with vacuities , lacuna, empty spaces, gaps, pits, vacuoles, vents, fissures. Most of the

particles have free space. These morphological features are controlled by the inspiration flow rate.

Example 14:

The experimental procedure and conditions used were the same as example 11, except that there was no vacuum hence the particles were not aspirated.

From Figure 25 it is evident that all the particles obtained are spheroidal in shape, smooth in surface texture with some particles having dimples. Comparing Figure 23 (where an inspiration flow rate is used) to that of Figure 25 (where an inspiration flow rate is NOT USED), indicates that atomising a liquid feedstock even if the liquid of that feed stock has high vapour pressure and hence high volatility , still does not allow the engineering of particles as shown in examples 11, 12 and 13 in which some of the casings are smooth in surface, some of the particle casing and interior are partially-permeable, permeable and impermeable, some of are riddled and riddled with vacuities , lacuna, empty spaces, gaps, pits, vacuoles, vents, fissures. Most of the particles have free space. These morphological features are controlled by the inspiration flow rate

The adopts the present invention relates to a process of engineering elegant particles and separating the elegant particles according to their aerodynamic diameter by the application of aspiration to generate a flow rate mimicking the inhalation flow rate of a patient . The process of the invention comprises:

-Adjusting the aspiration of a gas at controlled flow rate that is representative of patients inhalation flow rates.

-Subjecting solid particles or liquid droplets to the controlled aspiration flow rate to facilitate suspension and dispersion of said solid particles or liquid droplets

-Use of aspiration at the controlled flow rate to regulate the rate and extent of simultaneous and/or subsequent absorption, adsorption, desorption and combinations thereof, in any order, of liquid(s), vapour(s) and gas(es), from and/or to solid particles or liquid droplets, to initiate and or complete the formation of elegant aerodynamic particles whose morphological features are aspiration rate dependent.

-Use of the controlled aspiration flow rate to enable aerodynamic separation of the engineered elegant particles.

-Optionally, complete the formation of the engineered, elegant and aerodynamic particles

Testing the particles for their aerodynamic properties under the prevailing temperature and humidity conditions in the lungs of patients at that flow rate (need to include)

Testing the particles for their aerodynamic properties under the prevailing temperature and humidity conditions in the lungs of patients at different flow rates and subsequent changes in the particle morphological features.

Condition the surrounding gases at human lungs

Aspiration flow rate can be used to
Deaggregate liquid or solids.
Disperse solid particles or liquid droplets in a gaseous, vapour or liquid medium
Dictates the morphology and/or aerodynamic properties of the particles
Ensures the deposition of the particles according to their aerodynamic properties,
Provides a uniform agitation that is non-destructive facilitating particle growth with high degree of uniformity, monodispersity and crystallinity.
Enables the control of particle hollow volume.
Enables control of surface smoothness.

In one aspect of the present invention, provides a process for using aspiration to engineer elegant, aerodynamic and crystalline particles with defined morphological features from bulk powder in the wet or dry state, liquid droplet or bulk liquid or vapours.

The process of using bulk powder feedstock comprises;

1) Making available a feedstock powder, in dry or wet state, that is aspirated at a controlled flow rate matching that of a patient's inhalation inspiratory flow rate.
2) Using aspiration flow rate to facilitate deagglomeration, dispersion, transport , in a laminar or turbulent aspiratory flow and inspire said particles into at least one pre-separating zone which has at least one of the following roles;

a) Prevent bouncing and re-entrainment of agglomerated and non-inhalable particles
b) Facilitate desorption of gas, boiling gas, vapour or liquid and combinations thereof, from the airborne particles
c) Control the rate and extent of moisturising (by adsorption or absorption to) the airborne particle with the at least one or more boiling gas(es), vapour(s), liquid medium(s) and combinations thereof.

3) Using the aspiration flow rate to dictate the morphology and/or aerodynamic properties of the airborne particles by controlling the rate and extent of desorption of at least one gas, vapour or liquid , and combinations thereof, from said airborne particles
4) Allowing aspiration to drive and deposit the resulting particles according to their aerodynamic diameter at that flow rate.
5) Collecting and optionally drying said particles

The use of heat is not a necessity, however, moderate heat may be used to assist the aspiration flow rate to absorb, adsorb, desorb and combinations thereof, gas(es), boiling gas(es), vapour(s), liquid(s) and combinations thereof.

The morphology of the particle may facilitate absorption / adsorption / desorption on the inside and outer surfaces the particle especially where the particles are permeable to the absorbed / adsorbed and desorbed fluid. This allows restructuring of the inside and the outside of the particles rather than only the outside surface that is the case with non-permeable particles. The nature of the substance also plays an important role depending upon the affinity of the substance of the particle to the fluid that enabling diffusion of the fluid into the particle. The rate and extent of aspiration will control the surface texture of the particles to form such permeable particles that facilitate adsorption / absorption / desorption that restructures both the inside and the outside of the particles.

In another aspect of the current invention, collecting of the particles can occur by using the aspiration flow rate to uniformly deposit the resulting dispersed, particles into a crystallisation medium. This crystallisation medium is maintained under uniform non-destructive agitation by the uniform turbulence generated by the aspiration flow rate to enable instantaneous particle growth in a uniform manner

without interference and fusion of the particles and with high degree of mono-dispersity whilst ensuring the dispersion of individual particles during particle growth.

In another aspect of the present invention provides a process for using aspiration flow rate to control particle growth in a uniformly agitated and non-destructive environment to form uniformly shaped and sized monodisperse crystalline particles.

1) Making available a feedstock powder , in dry or wet state, that is aspirated at a controlled flow rate matching that of a patient's inspiratory flow rate.
2) Using aspiration to transport and inspire said particles into at least one pre-separating zone which has at least one of the following roles;
    a. Prevent bouncing and re-entrainment of agglomerated and non-inhalable particles
    b. Facilitate desorption of liquid from the airborne particles
    c. Control the rate and extent of moisturising (by adsorption or absorption to) the airborne particle with the at least one or more liquid medium(s).
3) Using the aspiration flow rate to dictate the morphology and/or aerodynamic properties of the airborne particles by controlling the rate and extent of desorption of at least one liquid from said airborne particles
4) Using a controlled aspiration flow rate to create uniform turbulence to non-destructively stir a crystallisation medium that facilitates and promotes particle growth in a uniform and dispersed manner to form monodisperse, non-cohesive and elegant particles of desired size.
5) Harvesting said particles.
6) Drying said particles.

In one aspect of the present invention, provides a process for using aspiration to engineer elegant, crystalline and aerodynamic particles from solid comprising;

6) Making available a feedstock powder that is aspirated at a controlled flow rate matching that of a patient's inspiratory flow rate.
7) Using aspiration to transport and inspire said particles into a pre-separating zone, that contains a liquid medium that has at least two roles
    a) Prevent bouncing and re-entrainment of agglomerated and non-inhalable particles
    b) Moisturise (by adsorption or absorption to) the airborne particle with the liquid medium.

8) Enabling the aspiration flow rate to control the rate and extent of desorption of the liquid from said airborne particles to initiate and/or form elegant, aerodynamic particles that match that flow rate.
9) Allowing aspiration to drive and deposit the engineered particles according to their aerodynamic diameter at that flow rate.
10) Collecting and optionally drying said elegant, aerodynamic particles

In another aspect of the present invention provides a process for using aspiration flow rate to simultaneously control particle morphology, particle crystallinity and particle aerodynamic diameter and thus deposition of said particles, the process comprises:

1) Making a substance available in droplet form and simultaneously aspirating said droplets at a controlled flow rate matching that of a patient's inspiratory inhalation flow rate
2) Enabling the aspiration flow rate to control the rate and extent of desorption of the liquid from the droplet to form particles of shape, surface texture and aerodynamic properties that match that flow rate.
3) Utilising the aspiration flow rate to convey and transport said particles over a liquid medium (located in a pre-separating chamber) that has at least two roles:
    a) Prevent bouncing and re-entrainment of agglomerated and non-inhalable particles
    b) Moisturise (by adsorption or absorption to) the airborne particle with the liquid medium.

    The aspiration flow rate facilitates partial or complete desorption of any remaining liquid present in the particles allowing ,at least, further improvement in particle crystallinity and/or particle shape and/or surface texture.
4) Allowing aspiration to drive and deposit the resulting particles according to their aerodynamic diameter at that flow rate.
5) Collecting and optionally drying said elegant, aerodynamic particles.

A further aspect of the present invention provides a process for using aspiration flow rate to engineer large(of any size), elegant particles with a high degree of monodispersity and uniformity, which can be used for example as a carrier. By dipping particles formed by the above processes or even liquid droplets in a liquid

medium contained in the collecting chamber. whilst maintained under the aspiration flow rate. The extent of particle growth depend on the degree of turbulence created by aspiration flow rate within the collecting chamber. The temperature may optionally be used to further facilitate the rate and extent of particle growth within the collecting chamber. The particles are harvested when the desired particle size and morphological characteristics are reached. The harvesting may be accomplished by the techniques known in the art such as filtration and the like. The harvested particles are dried using techniques known in the art.

The resulting particles from any aspect of the present invention may be further engineered by recycling them using any aspect of the present invention to ensure their aerodynamic suitability for that flow rate.

- Introducing liquid droplet or solid particles into an aspiration zone
- Aspirating said droplets or particles at a controlled flow rate to remove the solvent from droplets and or particles

Wherein the liquid is aspirated from the droplets at a controlled rate.
Engineering particles at
treating said particles or formed particles with a fluid
Classifying said particles or formed particles

The particles of the present invention were engineered under negative pressure created by act of inspiration at flow rates generated by patients with low, medium and high inspiratory flow rated that represent different patient airway conditions and patient type (i.e. children, elderly) that is representative of the end use situation.

The process further ensure the engineering of aerodynamic aerosol particles with high deposition in lower stages of the testing device (cascade impactor) coupled with high product yield

Engineering aerodynamic aerosols at flow rates that are representative of different patient and their airway conditions and thus inspiration airflow rate

Using negative pressure to engineer aerodynamic elegant aerosols under testing conditions which are representative of patient with different inspirations inhalation airflow rate, to engineer aerodynamic particles of suitable morphological features

Testing conditions will produce particles with different morphological feature that suit negative pressure used to generate them.

In conventional particle preparation for inhalers, it is automatically assumed that particles with geometric mean diameters 1-5microns are aerodynamically favourable. However the surface properties and bulk properties that cause imperfections such as cohesion, make these particles aerodynamically unfavourable. Additionally, there is no way of ensuring that the particles obtained during production are aerodynamically favourable.

The engineering device (testing equipment) can be any commercially available or otherwise conventional impactor that can be adapted to allow a vacuum or other gas into to generate an airflow through the testing device.

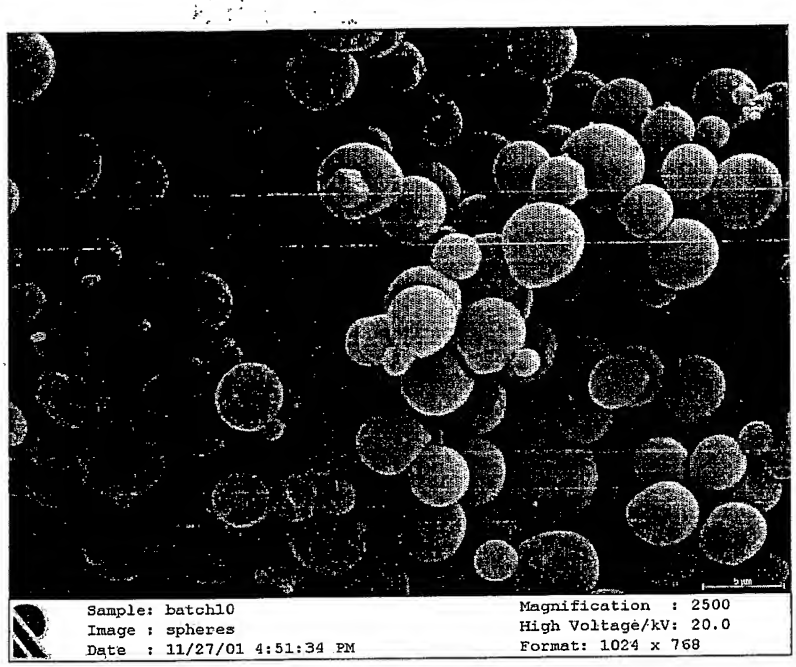
Aerosol is meant to indicate a suspension of solid or liquid particles in a gas- engineer- atomise particles of liquid as well as being useful to measure the particle size of atomises particles of solid.

Engineering:

Elegant aerodynamic particles with different morphological features that suit the inhalation flow used to generate them. The particles of the invention were engineered at a flow rate representative of the flow rate generated by different patients and patient airway conditions that is representative of the end use.

Engineering elegant aerodynamic particles that have different morphological feature that suit the inhalation flow rate generated by negative pressure of inspiration. The particles of the invention can be engineered at flow rate representative of different patients and their airway conditions that reflect the end use situation.

Aspirating solid particles or liquid droplets at a controlled inhalation flow rate to form an aerosol, that represent the flow rates of patients and their airway conditions to simultaneously or subsequently absorb, adsorb and /or desorb and combinations thereof, liquid vapour, gas from said solid particles or liquid droplets at a controlled aspiration flow rate to form elegant particles before and/or during and/or after separating said particles according to their aerodynamic diameter for that controlled flow rate.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Date : 11/27/01 4:51:34 PM
Magnification : 2500
High Voltage/kV: 20.0
Format: 1024 x 768

FIG. 1

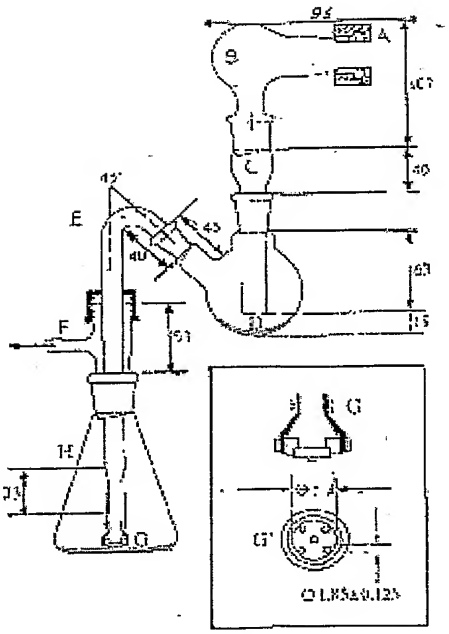

A
B
C
E
F
G
G'

FIG. 2

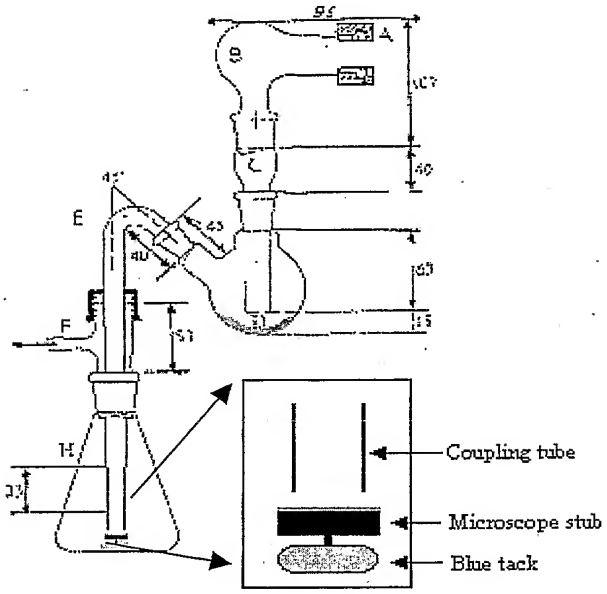


FIG. 3

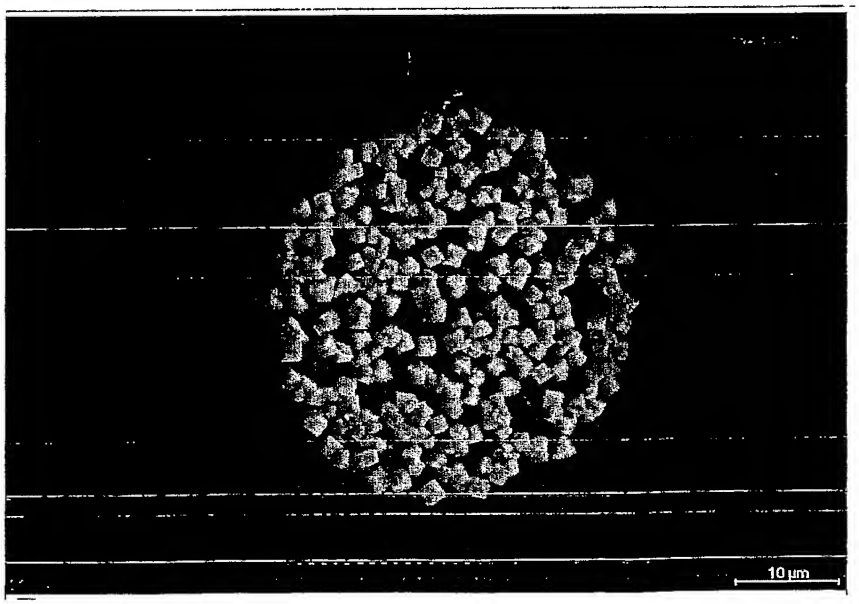


FIG. 4

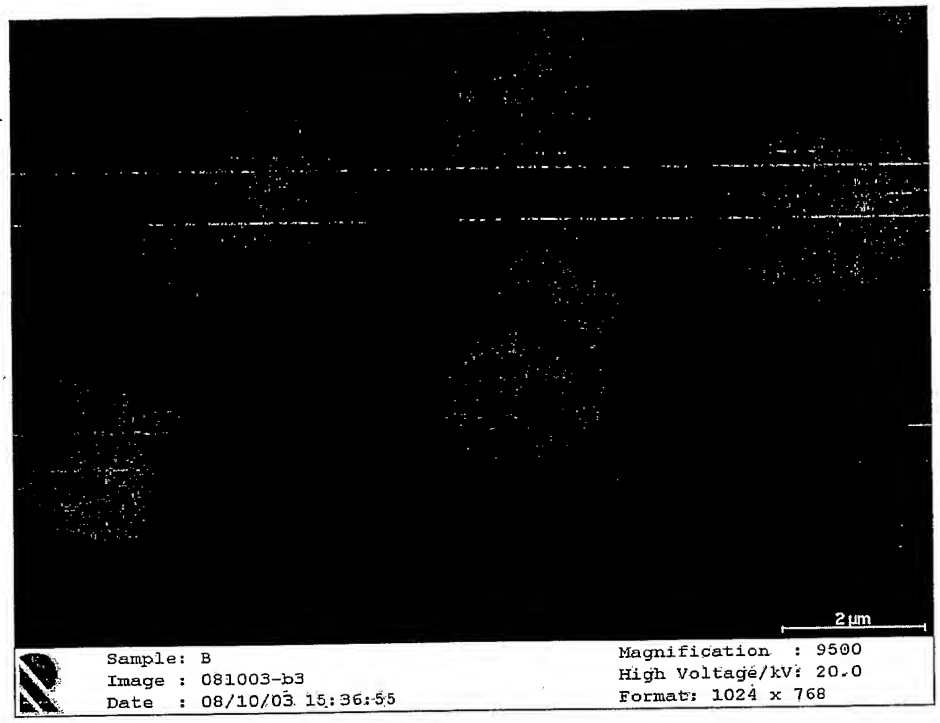

2 µm
Sample: B
Image : 081003-b3
Date : 08/10/03 15:36:55
Magnification : 9500
High Voltage/kV: 20.0
Format: 1024 x 768

FIG. 4.1

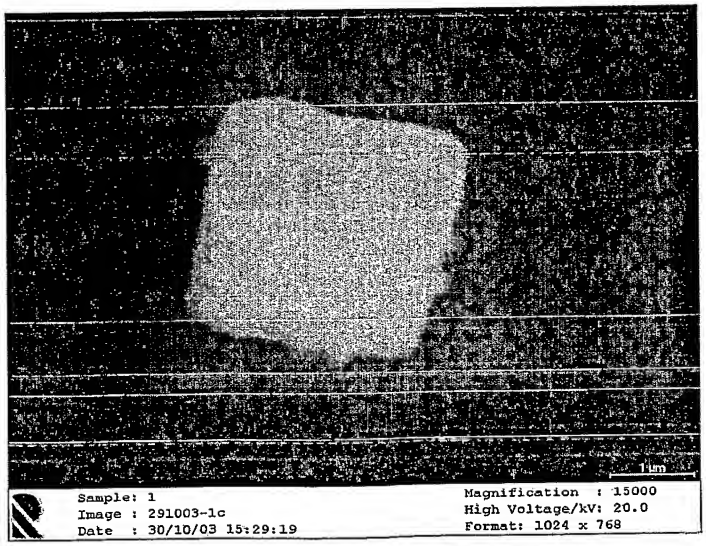

1 µm
Sample: 1
Image : 291003-1c
Date : 30/10/03 15:29:19
Magnification : 15000
High Voltage/kV: 20.0
Format: 1024 x 768

FIG. 5

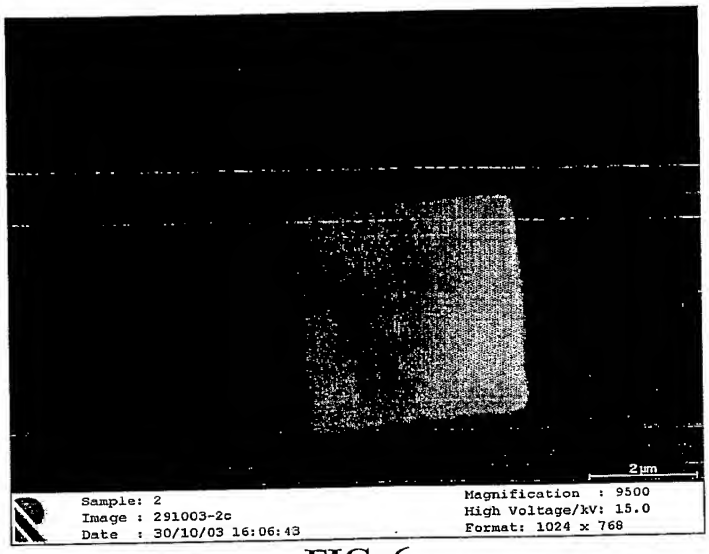

2µm
Sample: 2
Image : 291003-2c
Date : 30/10/03 16:06:43
Magnification : 9500
High Voltage/kV: 15.0
Format: 1024 x 768

FIG. 6

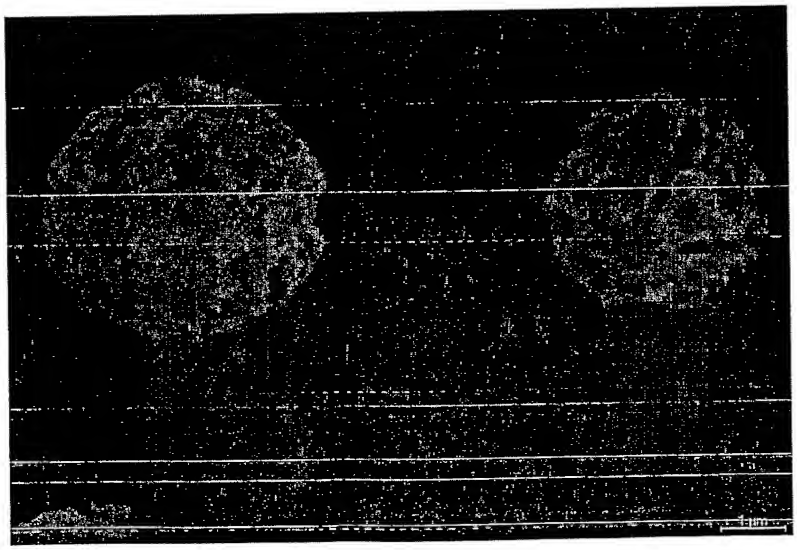
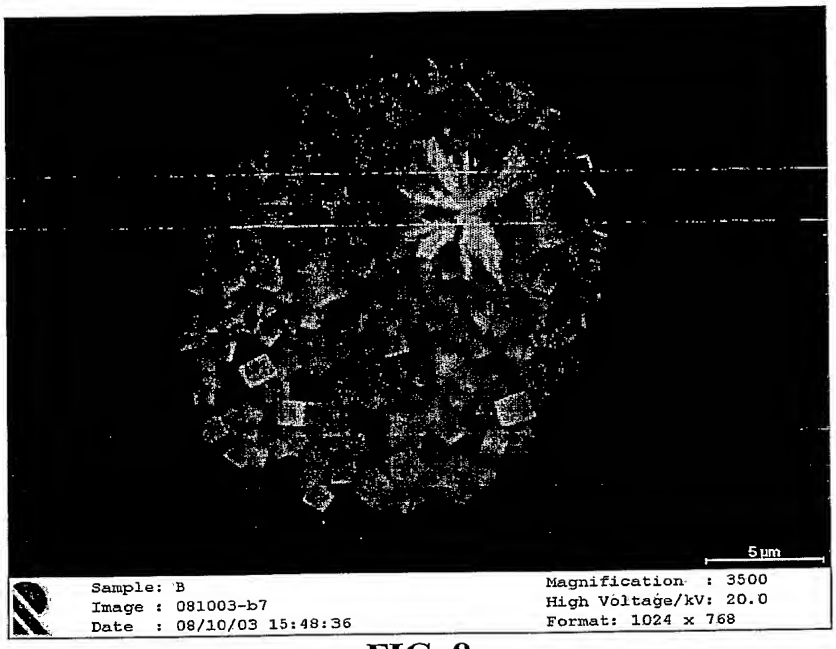


FIG. 7


5 µm
Sample: B
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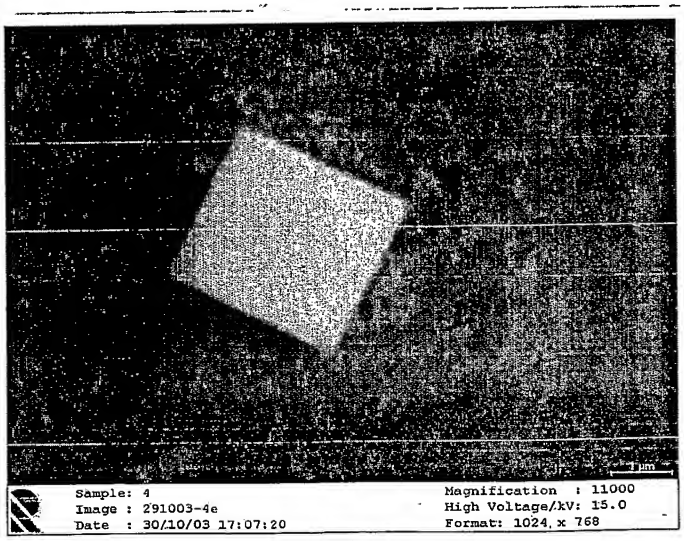
Magnification : 3500
High Voltage/kV: 20.0
Format: 1024 x 768

FIG. 8


1 µm
Sample: 4
Image : 291003-4e
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Magnification : 11000
High Voltage/kV: 15.0
Format: 1024 x 768

FIG. 9

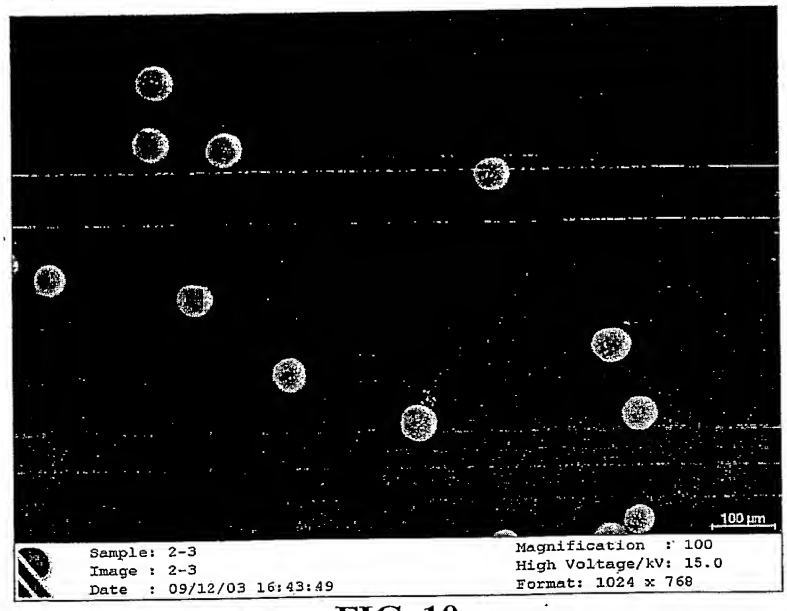


FIG. 10

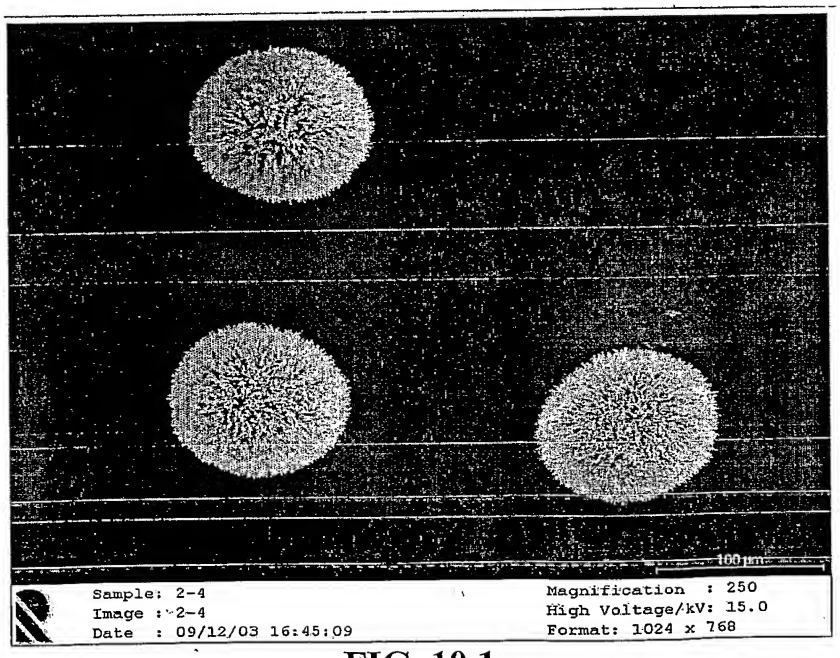
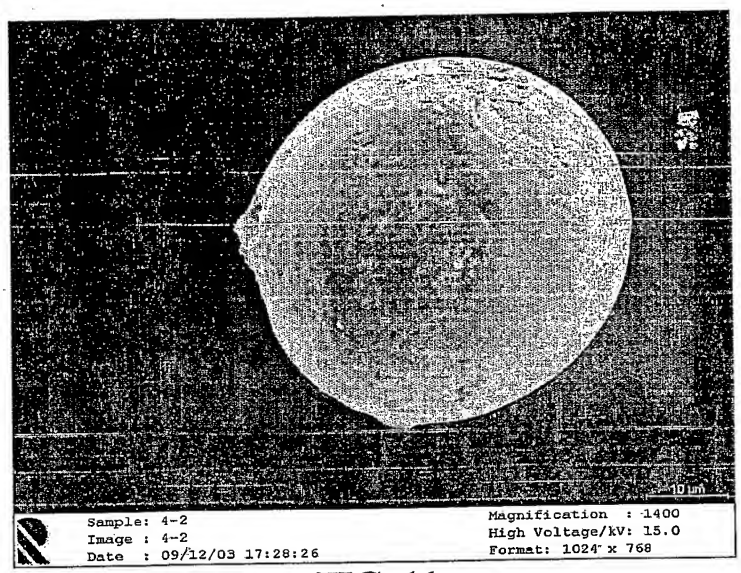


FIG. 10.1


10 µm
Sample: 4-2
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Magnification : 1400
High Voltage/kV: 15.0
Format: 1024 x 768

FIG. 11

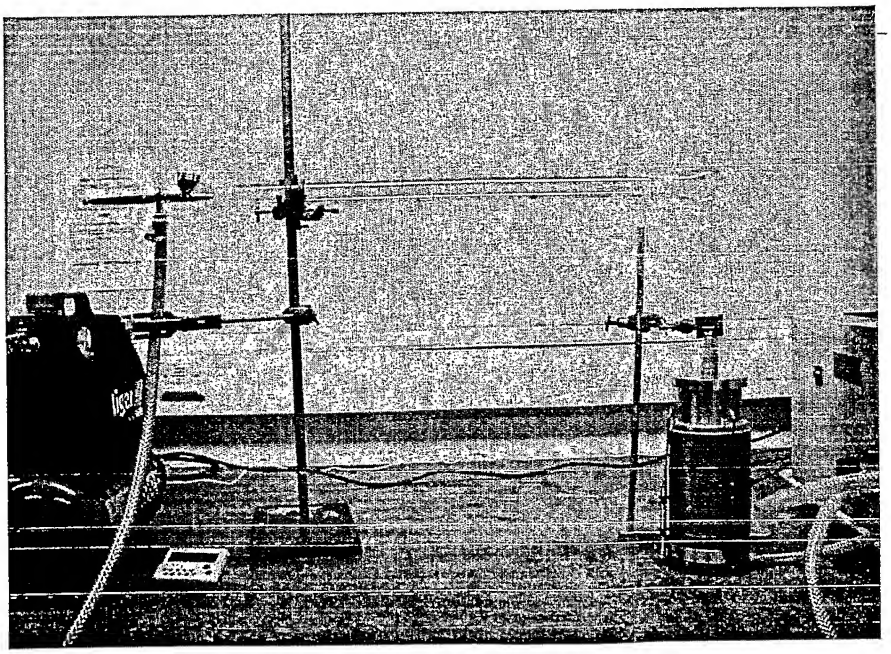
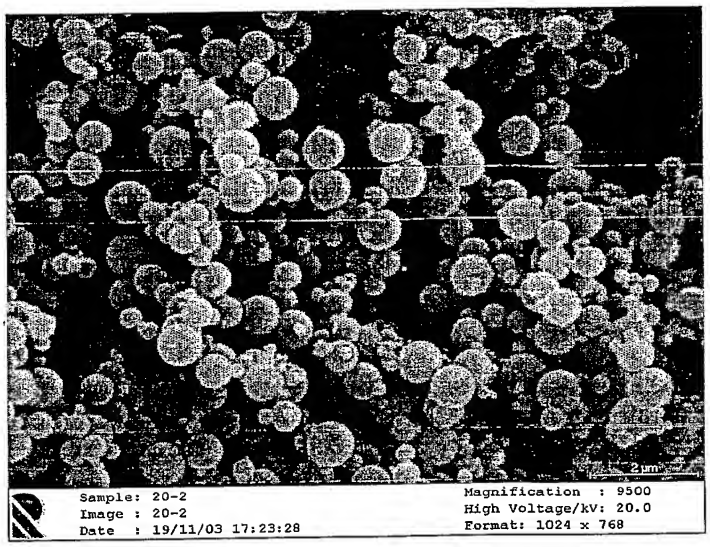


FIG. 12


Sample: 20-2
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Magnification : 9500
High Voltage/kV: 20.0
Format: 1024 x 768

FIG. 13

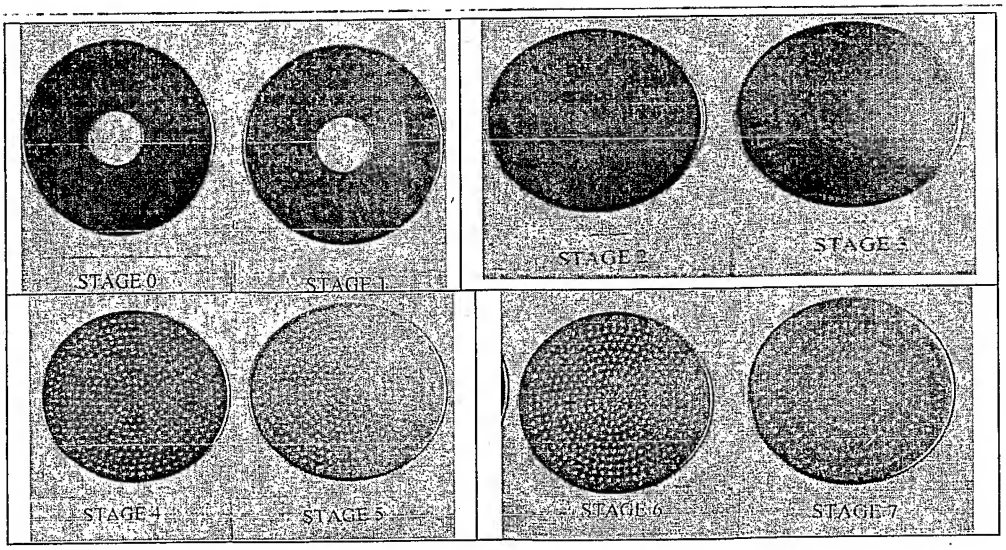
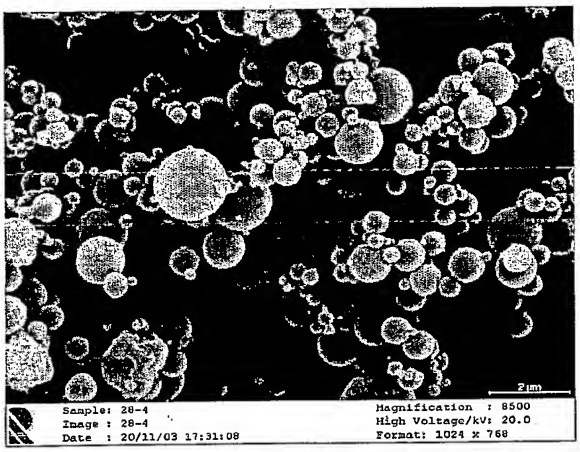

STAGE 0
STAGE 1
STAGE 2
STAGE 3
STAGE 4
STAGE 5
STAGE 6
STAGE 7

FIG. 14


2µm
Sample: 28-4
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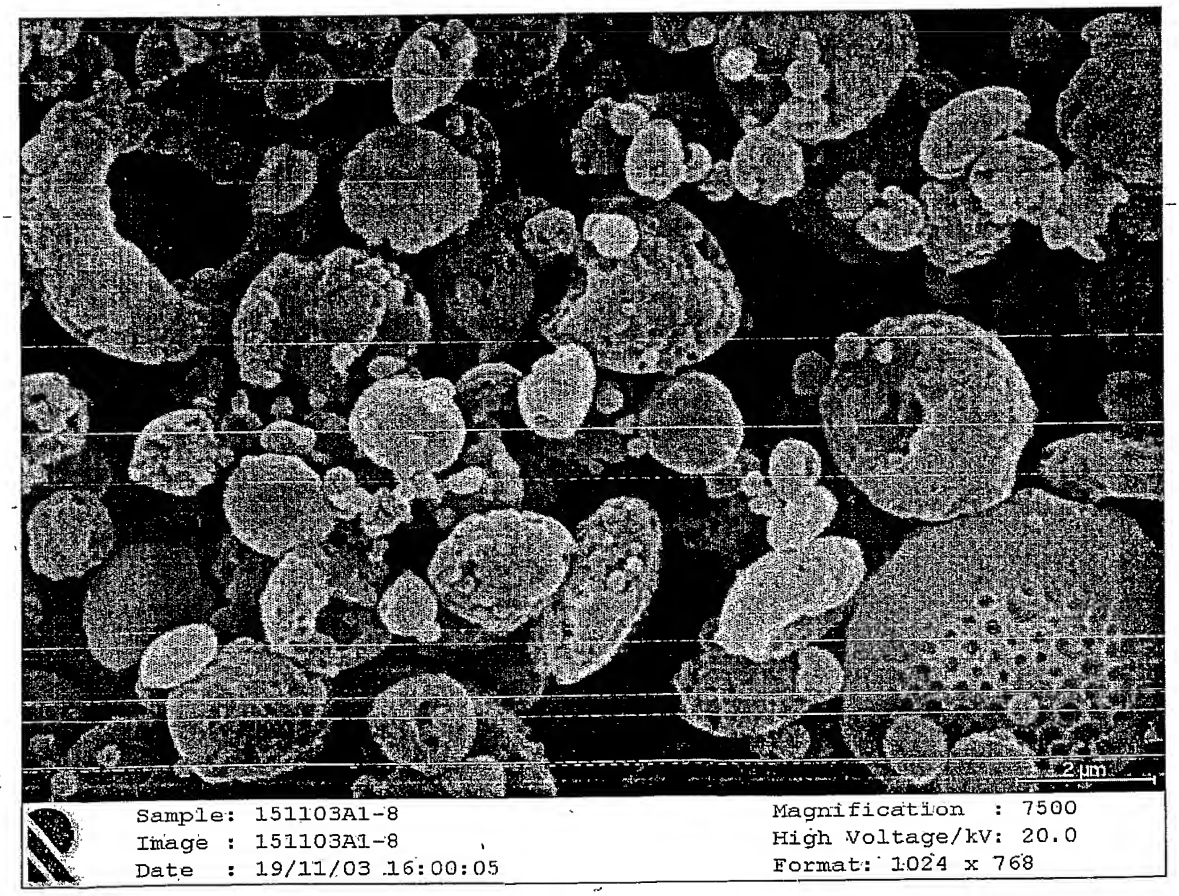
High Voltage/kV: 20.0
Format: 1024 x 768

FIG. 15


2 µm
Sample: 151103A1-8
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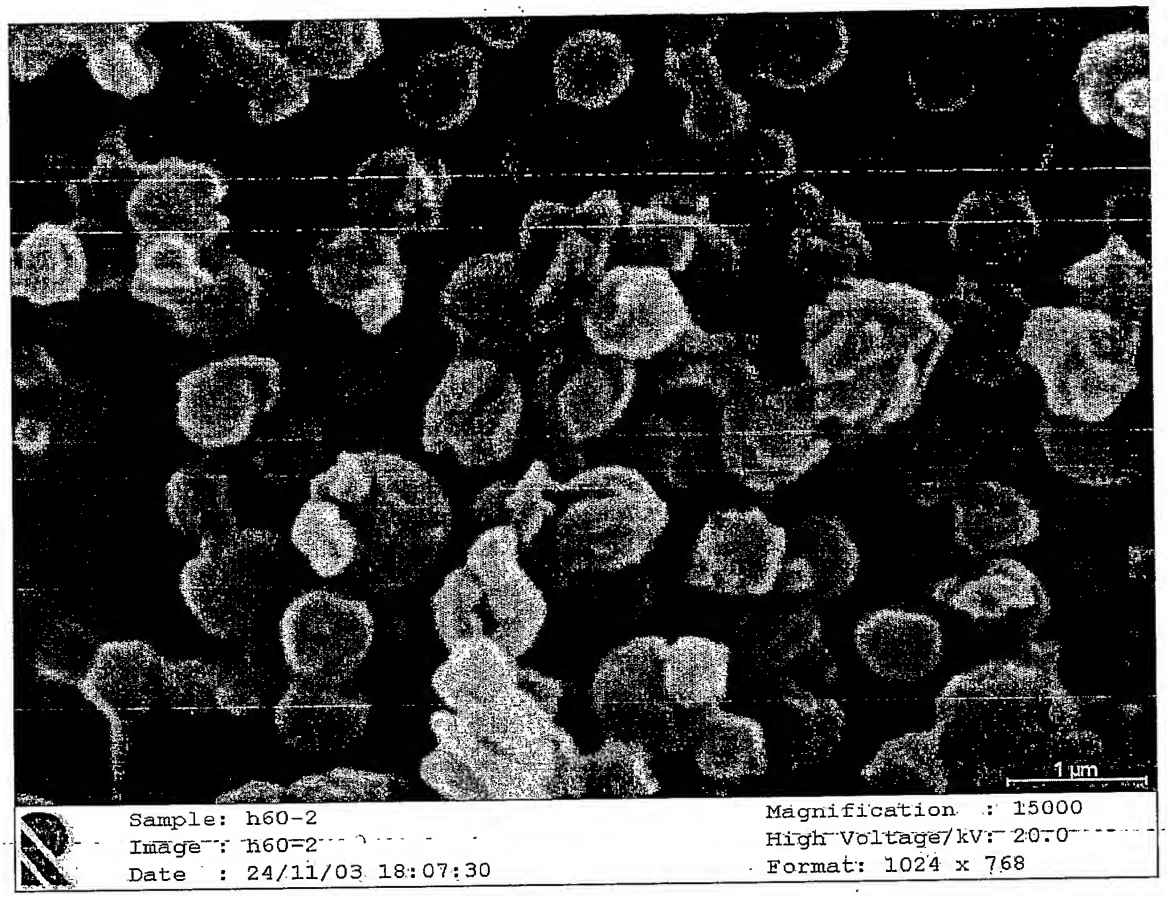
High Voltage/kV: 20.0
Format: 1024 x 768

FIG. 16


1 µm
Sample: h60-2
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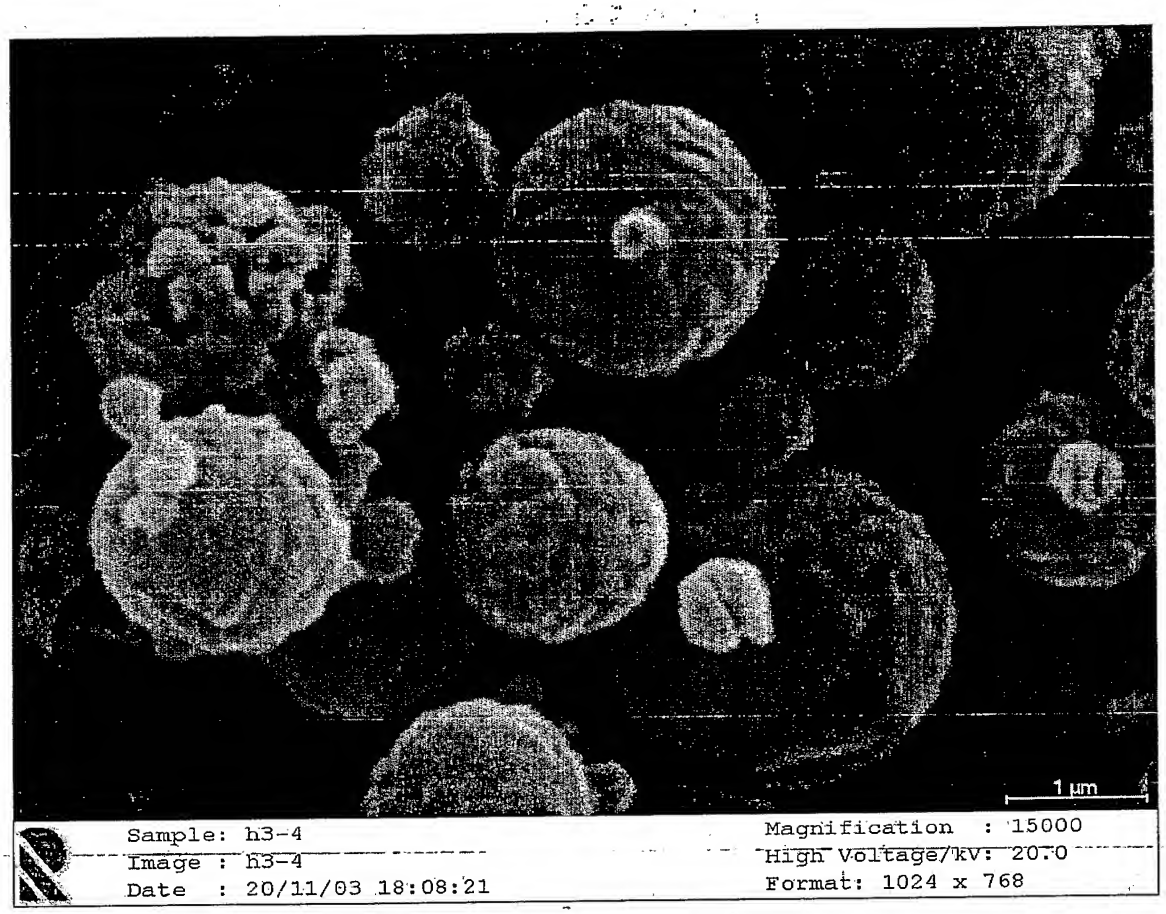
Date : 24/11/03 18:07:30
Magnification : 15000
High Voltage/kV: 20.0
Format: 1024 x 768

FIG. 17


1 µm
Sample: h3-4
Image : h3-4
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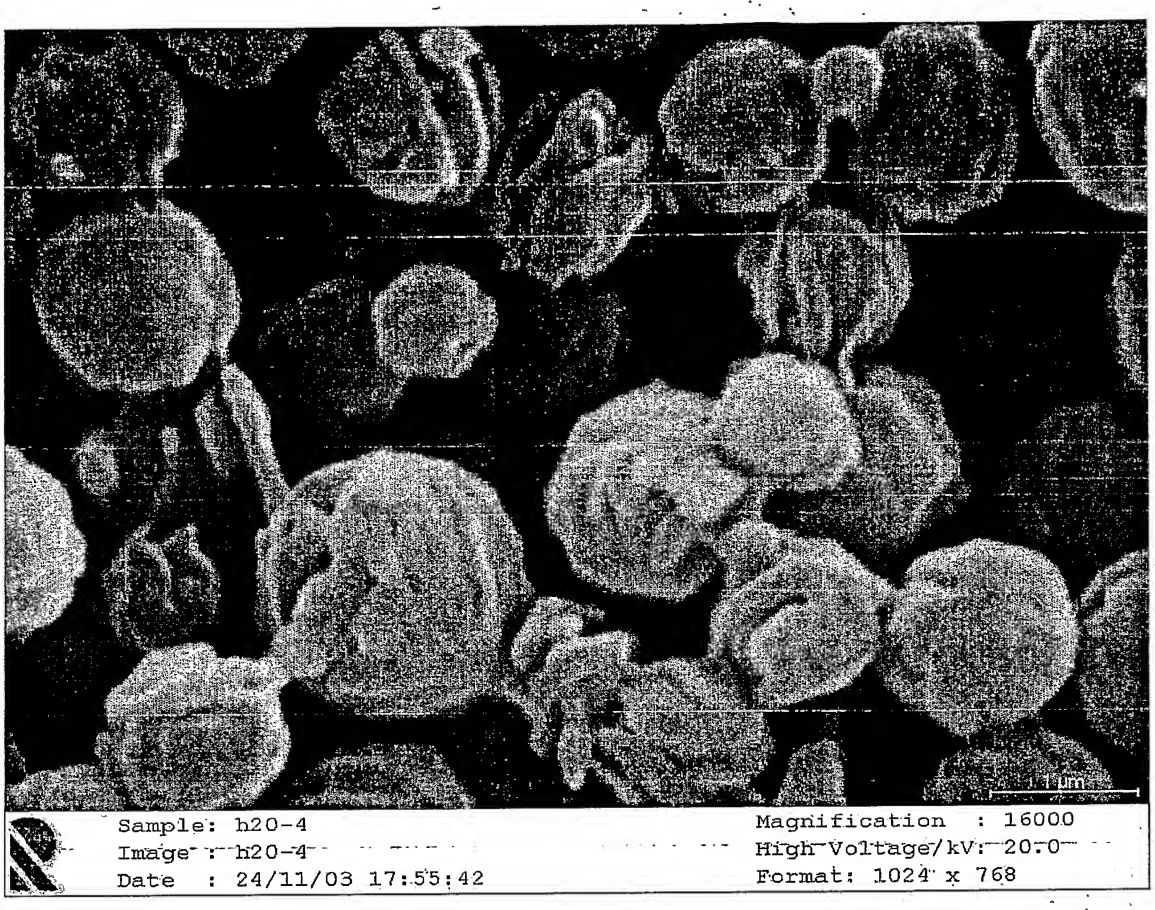
High Voltage/kV: 20.0
Format: 1024 x 768

FIG. 18


1 µm
Sample: h20-4
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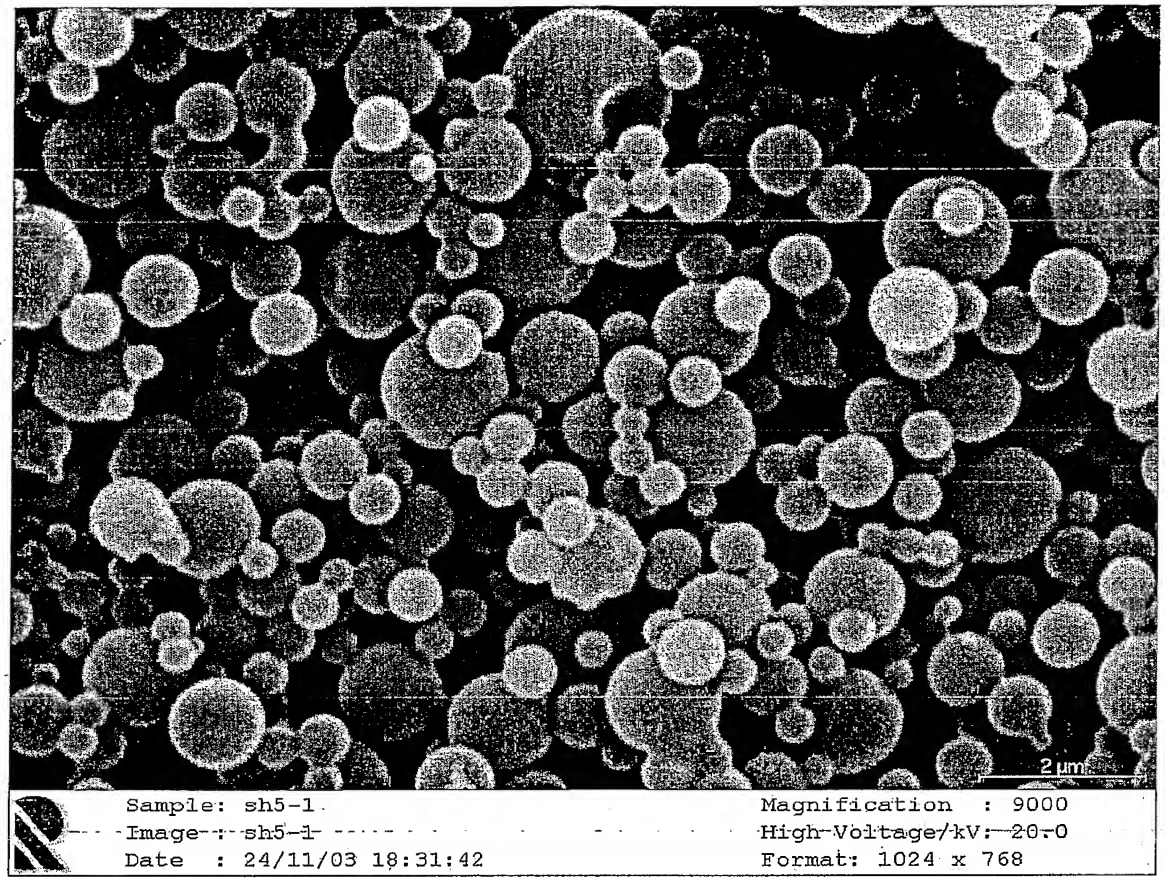
Magnification : 16000
High Voltage/kV: 20.0
Format: 1024 x 768

FIG. 19


2 µm
Sample: sh5-1
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Magnification : 9000
High Voltage/kV: 20.0
Format: 1024 x 768

FIG. 20

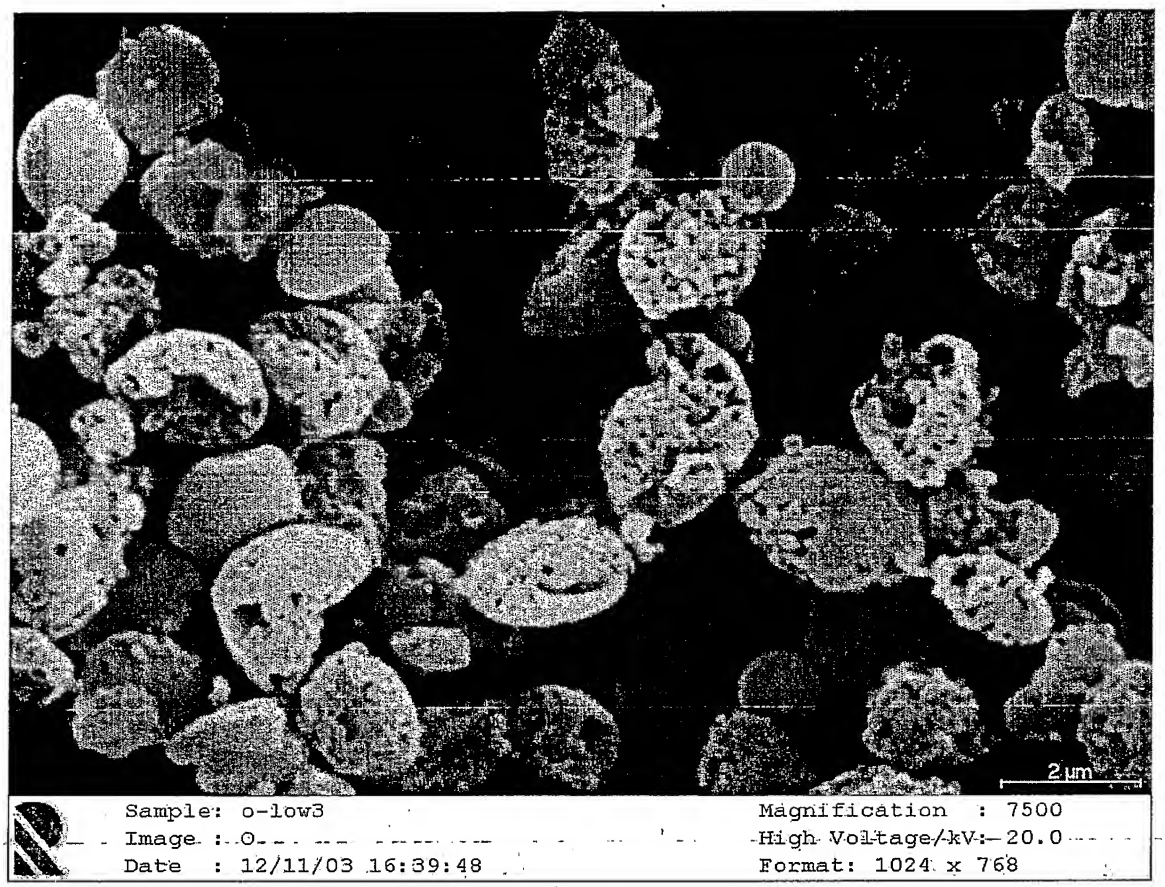
2 µm
Sample: o-low3
Image :
Date : 12/11/03 16:39:48
Magnification : 7500
High Voltage/kV: 20.0
Format: 1024 x 768

FIG. 22

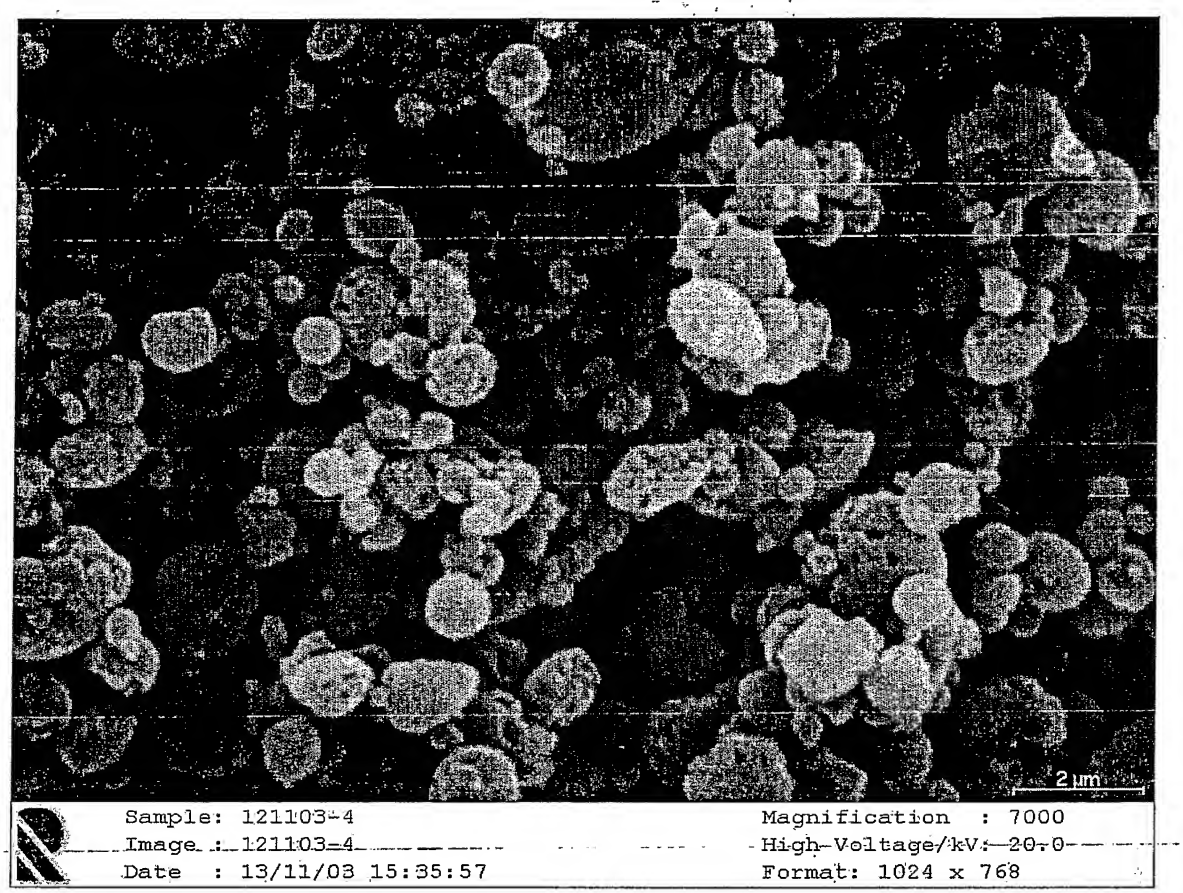

FIG. 23

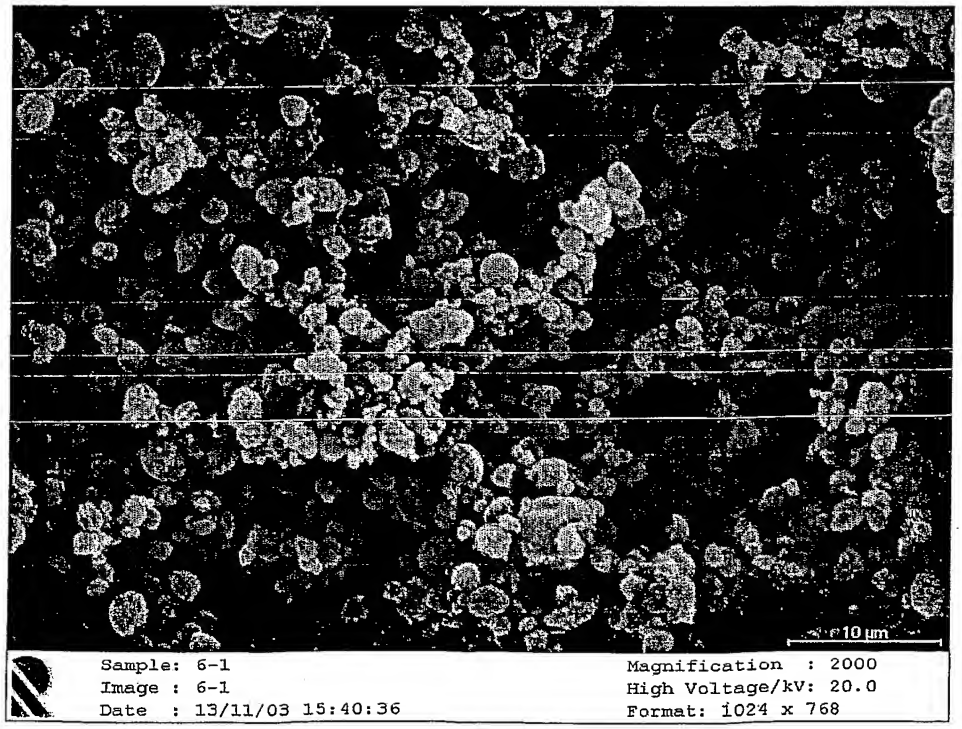

FIG. 24A

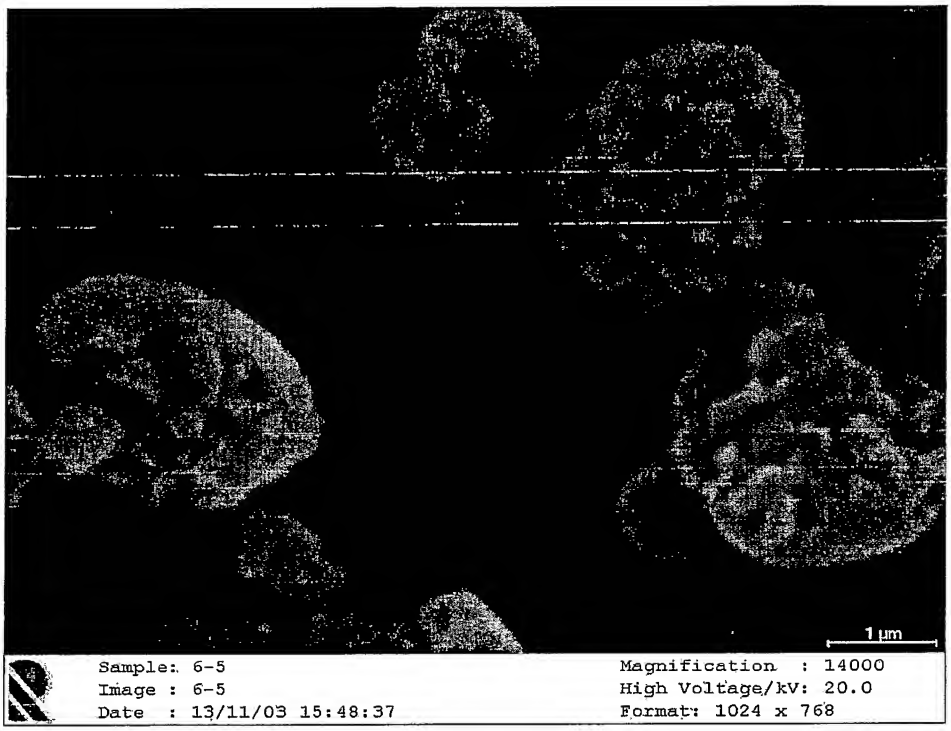

FIG. 24B

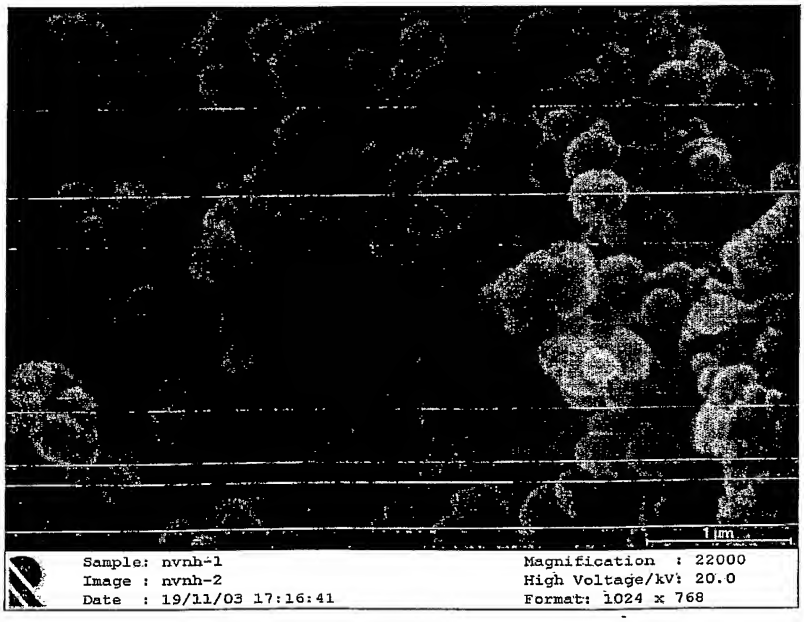

FIG. 25